

ABSTRACTS

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Fats

Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans.

Animal studies suggest that the 2 major omega3 fatty acids found in fish, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may have differential effects on blood pressure (BP) and heart rate (HR). The aim of this study was to determine whether there were significant differences in the effects of purified EPA or DHA on ambulatory BP and HR in humans. In a double-blind, placebo-controlled trial of parallel design, 59 overweight, mildly hyperlipidemic men were randomized to 4 g/d of purified EPA, DHA, or olive oil (placebo) capsules and continued their usual diets for 6 weeks. Fifty-six subjects completed the study. Only DHA reduced 24-hour and daytime (awake) ambulatory BP ($P < 0.05$). Relative to the placebo group, 24-hour BP fell 5.8/3.3 (systolic/diastolic) mm Hg and daytime BP fell 3.5/2.0 mm Hg with DHA. DHA also significantly reduced 24-hour, daytime, and nighttime (asleep) ambulatory HRs ($P = 0.001$). Relative to the placebo group, DHA reduced 24-hour HR by 3.5 \pm 0.8 bpm, daytime HR by 3.7 \pm 1.2 bpm, and nighttime HR by 2.8 \pm 1.2. EPA had no significant effect on ambulatory BP or HR. Supplementation with EPA increased plasma phospholipid EPA from 1.66 \pm 0.07% to 9.83 \pm 0.06% ($P < 0.0001$) but did not change DHA levels. Purified DHA capsules increased plasma phospholipid DHA levels from 4.00 \pm 0.27% to 10.93 \pm 0.62% ($P < 0.0001$) and led to a small, nonsignificant increase in EPA (1.52 \pm 0.12% to 2.26 \pm 0.16%). Purified DHA but not EPA reduced ambulatory BP and HR in mildly hyperlipidemic men. The results of this study suggest that DHA is the principal omega3 fatty acid in fish and fish oils that is responsible for their BP- and HR-lowering effects in humans. These results have important implications for human nutrition and the food industry.

Hypertension 1999 Aug;34(2):253-60

Gamma-linolenic acid dietary supplementation can reverse the aging influence on rat liver microsome delta 6-desaturase activity.

We have recently demonstrated that in rats the process of delta 6-desaturation of linoleic and alpha-linolenic acids slows with aging. One method of counteracting the effect of slowed desaturation of linoleic acid would be to provide the 6-desaturated metabolite, gamma-linolenic acid (18:3(n-6) GLA) directly. We have here investigated the 6-desaturation of both linoleic and alpha-linolenic acids in liver microsomes of young and old rats given GLA in the form of evening primrose oil (EPO) (B diet) in comparison to animals given soy bean oil alone (A diet), monitoring also the fatty acid composition of liver microsomes and relating this to the microviscosity of the membranes. In young rats the different experimental diets did not produce any difference in delta 6-desaturase (D6D) activity on either substrate suggesting that, when D6D activity is at or near its peak, the variations in diet tested are unable to influence it. In the old animals the rate of 6-desaturation of linoleic and particularly of alpha-linolenic acid was significantly greater in the B diet fed animals than in the A diet fed. The effects of the diets on the fatty acid composition of liver microsomes were consistent with the findings with regard to 6-desaturation. Administration of GLA partially corrected the abnormalities of n-6 essential fatty acid (EFA) metabolism by raising the concentration of 20:4(n-6) and other 6-desaturated EFAs. Furthermore, the GLA rich diet also increased the levels of dihomogamma-linolenic acid and of 6-desaturated n-3 EFAs in the liver microsomes. The microviscosity of microsomal membranes as indicated by DPH polarization was correlated with the unsaturation index of the same membranes. There was a very strong correlation between the two. In both young and old rats the B diet reduced the microviscosity and increased the unsaturation index. However, the effect was much greater in the old animals.

Biochim Biophys Acta 1991 May 8;1083(2):187-92

Health benefits of docosahexaenoic acid (DHA)

Docosahexaenoic acid (DHA) is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. The inclusion of plentiful DHA in the diet improves learning ability, whereas deficiencies of DHA are associated with deficits in learning. DHA is taken up by the brain in preference to other fatty acids. The turnover of DHA in the brain is very fast, more so than is generally realized. The visual acuity of healthy, full-term, formula-fed infants is increased when their formula includes DHA. During the last 50 years, many infants have been fed formula diets lacking DHA and other omega-3 fatty acids. DHA deficiencies are associated with foetal alcohol syndrome, attention deficit hyperactivity disorder, cystic fibrosis, phenylketonuria, unipolar depression, aggressive hostility and adrenoleukodystrophy. Decreases in DHA

in the brain are associated with cognitive decline during aging and with onset of sporadic Alzheimer disease. The leading cause of death in western nations is cardiovascular disease. Epidemiological studies have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction. The reduction is approximately 50% with 200 mg day⁻¹ of DHA from fish. DHA is the active component in fish. Not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias. The association of DHA deficiency with depression is the reason for the robust positive correlation between depression and myocardial infarction. Patients with cardiovascular disease or Type II diabetes are often advised to adopt a low-fat diet with a high proportion of carbohydrate. A study with women shows that this type of diet increases plasma triglycerides and the severity of Type II diabetes and coronary heart disease. DHA is present in fatty fish (salmon, tuna, mackerel) and mother's milk. DHA is present at low levels in meat and eggs, but is not usually present in infant formulas. EPA, another long-chain n-3 fatty acid, is also present in fatty fish. The shorter chain n-3 fatty acid, alpha-linolenic acid, is not converted very well to DHA in man. These longchain n-3 fatty acids (also known as omega-3 fatty acids) are now becoming available in some foods, especially infant formula and eggs in Europe and Japan. Fish oil decreases the proliferation of tumour cells, whereas arachidonic acid, a longchain n-6 fatty acid, increases their proliferation. These opposite effects are also seen with inflammation, particularly with rheumatoid arthritis, and with asthma. DHA has a positive effect on diseases such as hypertension, arthritis, atherosclerosis, depression, adult-onset diabetes mellitus, myocardial infarction, thrombosis and some cancers.

Pharmacol Res 1999 Sep;40(3):211-25

A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants.

The effects of dietary docosahexaenoic acid (DHA) supply during infancy on later cognitive development of healthy term infants were evaluated in a randomized clinical trial of infant formula milk supplemented with 0.35% DHA or with 0.36% DHA and 0.72% arachidonic acid (AA), or control formula which provided no DHA or AA. Fifty-six 18-month-old children (26 male, 30 female) who were enrolled in the trial within the first 5 days of life and fed the assigned diet to 17 weeks of age were tested using the Bayley Scales of Infant Development, 2nd edition (BSID-II) (Bayley 1993) at the Retina Foundation of the Southwest, Dallas, TX. These children had also been assessed at 4 months and 12 months of age for blood fatty-acid composition, sweep visual evoked potential (VEP) acuity, and forced-choice preferential looking (FPL) acuity (Birch et al. 1998). Supplementation of infant formula with DHA+AA was associated with a mean increase of 7 points on the Mental Development Index (MDI) of the BSID-II. Both the cognitive and motor subscales of the MDI showed a significant developmental age advantage for DHA- and DHA+AA-supplemented groups over the control group. While a similar trend was found for the language subscale, it did not reach statistical significance. Neither the Psychomotor Development Index nor the Behavior Rating Scale of the BSID-II showed significant differences among diet groups, consistent with a specific advantage of DHA supplementation on mental development. Significant correlations between plasma and RBC-DHA at 4 months of age but not at 12 months of age and MDI at 18 months of age suggest that early dietary supply of DHA was a major dietary determinant of improved performance on the MDI.

Dev Med Child Neurol 2000 Mar;42(3):174-81

Nimesulid

The in vitro effects of new non-steroidal antiinflammatory compounds on antioxidant system of human erythrocytes.

It has been reported by our group that some benzoxazolone and benzothiazolone derivatives showed significant antinociceptive and anti-inflammatory activity [DOGRUER et al. 1997]. It has been speculated that nonsteroidal anti-inflammatory drugs (NSAIDs) can act as the free radical scavengers and possess antioxidant activity. It is also well documented that oxidative stress can play an important role in the side effects of many xenobiotics including NSAIDs. Therefore, in the present study, the effects of six of the above mentioned benzoxazolone and benzothiazolone derivatives bearing 2-pyridylaminocarbonylmethyl moiety at the position 3 (I) on the antioxidant system-related parameters of human erythrocytes have been investigated. Diclofenac and nimesulid were also tested in the same systems as the control, because they are commonly used as NSAIDs. Our results showed that these compounds made significant changes in the antioxidant system of human erythrocyte.

Exp Toxicol Pathol 1999 Jul;51(4-5):397-402

Nimesulid and renal impairment.

OBJECTIVES: To analyse from spontaneous reporting data the renal adverse reactions associated with the use of nimesulid. **METHODS:** Case reports were obtained from a Northern Italian Regional database (Veneto Pharmacovigilance System), containing all the spontaneous reports filed between 1988 and 1997. The Veneto Region is the principal contributor to the Italian spontaneous reporting system, with an annual report rate of approximately 17 per 100,000 inhabitants. The clinical records of hospitalized patients were also analysed. **RESULTS:** Of the 120 reports associated with oral nimesulid, 11 referred to suspected renal adverse reactions. The drug was taken by ten patients for a short period. All the patients discontinued the therapy and hospitalization was required in six cases. Other risk factors were identified in six cases. **DISCUSSION:** Together with the new insights into the possible consequences of renal cyclooxygenase-2 (COX-2) inhibition, the reported cases should draw the attention of doctors and

patients to the importance of recognizing any possible signs of renal impairment during nimesulid therapy, although only extensive epidemiological data can define the real impact of its renal toxicity.

Eur J Clin Pharmacol 1999 Apr;55(2):151-4

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Thymosin alpha-1

High doses of thymosin alpha-1 enhance the anti-tumor efficacy of combination chemo-immunotherapy for murine B16 melanoma.

BACKGROUND: We have reported previously that combined chemo-immunotherapy with cyclophosphamide (CY), thymosin alpha-1 (T alpha-1) and low dose interferon alpha,beta (IFN alpha beta) has significant anti-tumour effects. Here, using mouse B16 melanoma as a model, we tested whether increasing the dose of T alpha-1 could increase the anti-tumour activity of triple combination chemo-immunotherapy. **MATERIALS AND METHODS:** C57BL/6 mice were challenged subcutaneously with B16 melanoma cells and injected intraperitoneally with saline, CY (200 mg/kg, day 7), or CY with T alpha-1 (200, 600 or 6000 micrograms/kg/day, days 10-13) and IFN alpha beta (30,000 I.U., day 13). **RESULTS:** Chemo-immunotherapy with high dose (HD)-T alpha-1 caused complete tumour regression for 27.5 days after tumour cell injection (3.9 times longer than untreated controls) and delayed tumour relapse compared to all other groups. Moreover, it significantly increased the median survival time of treated mice, and cured an average of 23% of animals, while none was cured in any other group. Splenocytes from HD-T alpha-1-treated mice showed markedly increased cytotoxic activities against both YAC-1 and autologous B16 tumour cells. HD-T alpha-1 treatment reversed the tumour-induced reduction in percentages of CD3 and CD4-positive splenocytes to non-tumour levels, and it increased percentages of CD8, B220 and IL-2R beta-positive cells to well beyond non-tumour controls. **CONCLUSIONS:** High doses of T alpha-1 improve anti-tumour efficacy of chemo-immunotherapy against B16 melanoma. These effects appear to be mediated by stimulation of the host immune response.

Cancer Res 1998 Sep-Oct;18(5A):3571-8

Thymosin alpha-1 is chemopreventive for lung adenoma formation in A/J mice.

The effects of thymosin (THN) alpha-1 were investigated using the urethane injection carcinogenesis A/J mouse model. Lung adenomas were observed 2.5, 3, and 4 months after urethane injection (400 mg/kg i.p.) into female A/J mice. Daily administration of THN alpha-1 (0.4 mg/kg, s.c.) reduced lung adenoma multiplicity significantly, by approximately 45, 40, and 17%, respectively, 2.5, 3 and 4 months after urethane injection. Animals treated with THN alpha-1 had a significantly greater white cell density than control A/J mice. Endogenous THN alpha-1-like peptides were detected in the mouse lung. By radioimmunoassay and by Western blot, prothymosin alpha was detected in the mouse lung. By immunocytochemistry, THN alpha-1-like peptides were detected in all lung compartments including the bronchus, adenoma, bronchioles, and alveoli. These results indicate that exogenous THN alpha-1 prevents lung carcinogenesis in A/J mice.

Cancer Lett 2000 Jul 31;155(2):121-7

Immunomodulating activity of thymosin fraction 5 and thymosin alpha-1 in immunosuppressed mice.

We found that both thymosin from calf thymus and its constituent peptide alpha-1 prepared by chemical synthesis restore cell-mediated immunity following its suppression in mice by injection of 5-FU. Conditions suitable for assessing the thymosin activity by means of footpad reaction were established in such immunosuppressed mice. In this new animal model, thymosin alpha-1 peptide showed activity at a low dose of 5-50 micrograms/kg, which was 100-1,000 times less than that required for thymosin F-5 preparations. Further studies utilizing the adoptive transfer technique showed that alpha-1 peptide corrects the 5-FU-induced suppression of mature T cells, transferring the DTH response as well as that of macrophage function responsible for the expression of footpad reaction. Furthermore, regeneration of lymph node and bone marrow cells as well as CFU-c (progenitor cells of macrophages and granulocytes) was enhanced by thymosin alpha-1 in the 5-FU-treated mice. All these results indicate that thymosin alpha-1 accelerates the replenishment and maturation of haematopoietic cells, including not only T cells but also macrophages, when they have been severely damaged by the 5-FU treatment.

Cancer Immunol Immunother 1983;15(2):108-13

Thymosin alpha-1 exerts protective effect against the 5-FU induced bone marrow toxicity.

Thymosin alpha-1 was shown to prevent the 5-fluorouracil (5-FU)-induced bone marrow toxicity in BDF1 mice, as determined by the cellularity, haemopoietic stem cells (CFU-s) and granulocyte-macrophage colony forming unit (GM-CFU). Furthermore, thymosin alpha-1 increased the levels of colony stimulating factor (CSF) in sera or in culture media of spleen cells derived from 5-FU-treated mice. The treatment of spleen cells with anti-Thy 1,2 antibody plus complement abolished completely the CSF

production. The in vivo treatment of donor mice with anti-Thy 1,2 antibody following 5-FU abolished completely the capability of their bone marrow cells to save lethally irradiated recipients. Thymosin alpha-1 treatment prevented the damage by such combined treatment. The present study indicates that thymosin alpha-1 exerts its protective effect against the 5-FU-induced bone marrow toxicity, at least partially, through its effect on the maturation of immature T cells to functional T cells which produce various kinds of lymphokines including CSF.

Int J Immunopharmacol 1985;7(5):761-8

Combination thymosin alpha-1 and lymphoblastoid interferon treatment in chronic hepatitis C.

BACKGROUND: Monotherapy for chronic hepatitis C using interferon (IFN) results in a very small proportion of patients exhibiting a sustained response. Clinical trials assessing the benefit of combination drug therapy may provide evidence of improved treatment response over that seen with single drug treatment. **AIM:** To assess the response in patients with chronic hepatitis C to one year of combination treatment: thymosin alpha-1 (T alpha-1), 1 mg twice weekly, and lymphoblastoid (L)-IFN, 3 MU thrice weekly. **PATIENTS AND METHODS:** Fifteen patients with serum HCV RNA positive chronic hepatitis C were studied. Eleven patients were treatment naive and four had failed previous standard IFN therapy. Thirteen patients were HCV RNA serotype 1b. All patients were given combination T alpha-1 and L-IFN therapy for one year with a six month follow up period. **RESULTS:** Six months after initiation of treatment seven patients (47%) were sera HCV RNA negative and at completion of the one year treatment 11 (73%), including two who had failed previous standard IFN treatment, had negative serum HCV RNA. Six months after treatment, six patients (40%), including five with HCV type 1b, showed a sustained response characterized by a negative serum HCV RNA. **CONCLUSIONS:** The results of this open label trial suggest that there may be a potential benefit to combining an immune modulator (T alpha-1) with an antiviral (IFN) in the treatment of chronic hepatitis C. Verification of the observations in this study require completion of a randomised controlled study.

Gut 1996 Nov;39(5):679-83

Memantine

Pharmacologic rationale for memantine in chronic cerebral hypoperfusion, especially vascular dementia.

Memantine is a moderate-affinity, voltage-dependent, uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors. In contrast to competitive NMDA antagonists, memantine is well tolerated in humans and is being developed for the treatment of dementia. The pathogenesis of vascular dementia (VaD) is largely unknown, and is likely multifactorial, but it involves the impairment of blood circulation as a common denominator. There is broad evidence for the efficacy of memantine in several animal models of ischemia. Memantine also acts on several secondary, potentially contributing factors in VaD such as neuronal depolarization, removal of magnesium block of NMDA receptors, chronic overstimulation of these receptors, and, possibly, mitochondrial dysfunction. Among others, it also has additional positive effects on long-term potentiation and cognition in standard animal models of impaired synaptic plasticity. Recently, clinical efficacy of memantine has been shown in an etiologically mixed population of severely demented patients, including those with VaD. Given the difficulties of diagnosing VaD in clinical practice, an optimal antidementive drug should be beneficial in both Alzheimer disease and VaD. Preclinical data presented in this paper indicate that such benefits can be achieved with memantine. In addition, phase II clinical data in dementia are summarized, and two ongoing pivotal trials in VaD are described. Suggestions for VaD guideline development are made regarding clinical instruments, and etiologies and severity stages are considered.

Alzheimer Dis Assoc Disord 1999 Oct-Dec;13 Suppl 3:S172-8

Efficacy and tolerability of memantine in patients with dementia syndrome. A double-blind, placebo controlled trial.

The efficacy and tolerability of memantine (1-amino-3,5-dimethyl-adamantane hydrochloride, Akatinol memantine; CAS 41100-52-1) was investigated in a double-blind, randomized clinical study versus placebo in 66 patients aged between 65 and 80 years predominantly suffering from mild to moderate vascular dementia. The target variables assessed were the baseline differences of the Sandoz Clinical Assessment Geriatric scale (SCAG) and Syndrom-Kurz-Test (SKT) total scores and the total time required in the subtests of Activity of Daily Living tests (ADL). Additional parameters assessed were the physician's global impression, the Mini Mental State Evaluation (MMSE), the Tapping and Trace tests for fine motor rating and the quality in performing the ADL tests. Adverse drug effects were recorded by DOTES/TWIS. 59 of the 66 patients included in the study terminated the trial (29 in the placebo and 30 in the memantine group). For the baseline differences of the SCAG total score a statistically significant improvement was observed already after 14 days of memantine treatment as compared to placebo. After 42 days this difference was still more pronounced and highly significant. Significant improvements after 14 and 42 days of memantine treatment could also be demonstrated for the SCAG subscales cognitive disturbances, lack of drive, emotional disturbances, social behaviour and somatic disturbances. Additionally, the efficacy of the drug could be confirmed by the SKT and ADL tests. Particularly striking in the ADL tests was the considerable improvement achieved in the quality of performing the tasks under memantine treatment.

Evaluation of memantine for neuroprotection in dementia.

Memantine, a non-competitive NMDA antagonist, has been approved for use in the treatment of dementia in Germany for over ten years. The rationale for use is excitotoxicity as a pathomechanism of neurodegenerative disorders. memantine acts as a neuroprotective agent against this pathomechanism, which is also implicated in vascular dementia. HIV-1 proteins Tat and gp120 have been implicated in the pathogenesis of dementia associated with HIV infection and the neurotoxicity caused by HIV-1 proteins can be blocked completely by memantine. memantine has been investigated extensively in animal studies and following this, its efficacy and safety has been established and confirmed by clinical experience in humans. It exhibits none of the undesirable effects associated with competitive NMDA antagonists such as dizocilpine. The efficacy of memantine in a variety of dementias has been shown in clinical trials. Memantine is considered to be a promising neuroprotective drug for the treatment of dementias, particularly Alzheimer's disease for which there is no neuroprotective therapy available currently. It can be combined with acetylcholinesterase inhibitors which are the mainstay of current symptomatic treatment of Alzheimer's disease. Memantine has a therapeutic potential in numerous CNS disorders besides dementias which include stroke, CNS trauma, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), epilepsy, drug dependence and chronic pain. If memantine is approved by the FDA for some of these indications by the year 2005, it can become a blockbuster drug by crossing the US \$1 billion mark in annual sales.

Expert Opin Investig Drugs 2000 Jun;9(6):1397-406

Effects of oral memantine administration on Parkinson symptoms. Results of a placebo-controlled multicenter study.

The effectiveness of memantine on the symptoms of Parkinson's disease was investigated in 67 patients (39 males, 28 females) mostly between 55 and 75 years. The study was multi-center placebo-controlled with four treatment groups, i. e. patients with and without pre- and after-treatment with other anti-Parkinson medication receiving either placebo or memantine as sole or additional medication. The analysis of 61 evaluable cases showed a positive statistically significant influence on the single symptom tremor as well as on the neurological overall symptomatology (Webster-scale total score). Despite the inadequately ascertained mode of action memantine promises success particularly in milder and initial forms of the Parkinson syndrome either used as monotherapy or as an adjuvant.

Dtsch Med Wochenschr 1984 Jun 22;109(25):987-90

Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine).

OBJECTIVES: To assess clinical efficacy and safety of memantine-an uncompetitive N-methyl-D-aspartate (NMDA) antagonist-in moderately severe to severe primary dementia. **MATERIALS AND METHODS:** Dementia was defined by DSM-III-R criteria and severity was assessed by the Global Deterioration Scale (stages 5-7) and the Mini-Mental State Examination (< 10 points). Primary endpoints were the Clinical Global Impression of Change (CGI-C) rated by the physician, and the Behavioural Rating Scale for Geriatric Patients (BGP), subscore 'care dependence', rated by the nursing staff. Secondary endpoints included the modified D-Scale (Arnold/Ferm). **RESULTS:** The ITT sample comprised 166 patients and 151 patients were treated per protocol. At 12-week ITT endpoint analysis, 82 received memantine 10 mg per day, 84 placebo. Dementia was in 49% of the Alzheimer type and in 51% of the vascular type (CT, Hachinski score). A positive response in the CGI-C was seen in 73% versus 45% in favour of memantine (stratified Wilcoxon $p < 0.001$), independent of the etiology of dementia. The results in the BGP subscore 'care dependence' were 3.1 points improvement under memantine and 1.1 points under placebo ($p = 0.016$). A coincident response of the two independent target variables was observed in 61.3% (memantine) versus 31.6% (placebo). Secondary endpoint analysis of the D-Scale assessing basic ADL functions support the primary results. Regarding the safety profile, no significant differences between treatment groups were observed. **CONCLUSIONS:** The results of this trial support the hypothesis that memantine treatment leads to functional improvement and reduces care dependence in severely demented patients.

Int J Geriatr Psychiatry 1999 Feb;14(2):135-46

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