ELDOR-001 US PROV

INTRALIPID FOR THERAPY

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FIELD OF THE INVENTION

[0001] The present invention relates in general to intralipid and its use in therapy. Specifically, the present invention relates to the use of intralipid for treating Alzheimer's disease and postoperative delirium (POD), and methods of treatment thereof.

SUMMARY OF THE INVENTION

[0002] Currently, there is no cure for Alzheimer's disease. But drug and non-drug treatments may help with both cognitive and behavioral symptoms. Researchers are looking for new treatments to alter the course of the disease and improve the quality of life for people with dementia (1). The present invention is the first to suggest intralipid treatment for the treatment of Alzheimer disease. In certain embodiments, intralipid should be given intravenously on a monthly basis according to each patient's individual response.

DETAILED DESCRIPTION OF THE INVENTION

Intralipid for Treating Alzheimer's Disease

[0003] Dr. Aloysius "Alois" Alzheimer was a German psychiatrist and neuropathologist and a colleague of Emil Kraepelin. Alzheimer is credited with identifying the first published case of "presenile dementia", which Kraepelin would later identify as Alzheimer's disease (2).

[0004] In 1901, Dr. Alzheimer observed a patient at the Frankfurt Asylum named Auguste Deter. The 51-year-old patient had strange behavioral symptoms, including a loss of short-term memory; she became his obsession over the coming years. Auguste Deter was a victim of the politics of the time in the psychiatric community; the Frankfurt asylum was too expensive for her husband. Mr. Deter made several requests to have his wife moved to a less expensive facility, but Dr. Alzheimer intervened in these requests. Ms. Deter remained at the Frankfurt asylum, where Alzheimer had made a deal to receive her records and brain upon her death (3). On 8 April 1906, Ms. Deter died, and Dr. Alzheimer had her medical records and brain brought to Munich where he was working in Kraepelin's laboratory. With two Italian physicians, he used the staining techniques of Bielschowsky to identify amyloid plaques and neurofibrillary tangles. These brain anomalies would become identifiers of what later became known as Alzheimer's Disease (4).

Alzheimer's disease

[0005] Some evidence indicates that disruption of the blood-brain barrier (BBB) in Alzheimer's disease patients allows blood plasma containing amyloid beta (Aβ) to enter the brain where the Aβ adheres preferentially to the surface of astrocytes (5). These findings have led to the hypotheses that (1) breakdown of the BBB allows access of neuronbinding autoantibodies and soluble exogenous $A\beta_{42}$ to brain neurons and (2) binding of these autoantibodies to neurons triggers and/or facilitates the internalization and accumulation of cell surface-bound $A\beta_{42}$ in vulnerable neurons through their natural tendency to clear surface-bound autoantibodies via endocytosis. Eventually the astrocyte is overwhelmed, dies, ruptures, and disintegrates, leaving behind the insoluble $A\beta_{42}$ plaque. Thus, in some patients, Alzheimer's disease may be caused (or more likely, aggravated) by a breakdown in the blood–brain barrier (6).

[0006] AD evolves with widespread loss of neurons and their synapses in such key brain areas as the cerebral cortex, entorhinal area, and hippocampus. At the gross level, this is evident as a general shrinkage of the brain away from the cranial vault and a corresponding dilation of the fluid-filled brain ventricles to fill the void. At the microscopic level, there are several different pathological changes that occur, but one consistent pathological hallmark is the early appearance of amyloid plaques. These plaques are abundant and widely scattered throughout AD-vulnerable brain regions. They contain a 42-amino acid protein fragment, known as amyloid 1-42 (A_{42}), that is derived from the sequential enzymatic cleavage of the much larger amyloid precursor protein. Once produced, A_{42} has the ability to self-assemble into nondegradeable fibrils that can persist in AD brains long after the neurons in which they accumulated have died (7).

[0007] Alzheimer’s disease (AD) was first described in 1906 by German psychiatrist Alois Alzheimer, who observed abnormal clumps and tangled bundles of protein in the brain of a patient who experienced memory loss, language difficulties, and abnormal behaviour (8). The risk of developing AD increases exponentially with age and is the leading cause of dementia and the most common neurodegenerative disease in the elderly; prevalence rates in 65-74 year olds are estimated to be 3%, rising to 19% for 75-85 year olds, and nearly 50% in those aged over 85 (9). AD is more common among older people but it is not a normal part of ageing. As the global population ages, the prevalence of AD is expected to rise from 36 million to 115 million sufferers by 2050 (9).

[0008] It is estimated that over 5% of the US population over 65 and over 15% of the U.S. population over 85 are beset with some form of Alzheimer's disease (10). It is believed that the

principal cause for confinement of the elderly in long term care facilities is due to this disease, and approximately 65% of those dying in skilled nursing facilities suffer from it (11).

Intravenous lipid emulsion

[0009] The idea that intravenous lipid emulsion could be used to affect the pharmacokinetics of a drug in circulation was first introduced fifty years ago. It was shown that rats infused lipid emulsion after an injection of the barbiturate thiopental emerged more rapidly from anaesthesia than rats infused the same volume of fat-free solution (Russell & Westfall 1962) (12). Other early studies were published on the effect of lipid emulsion on chlorpromazine availability in rabbits (13), and the effect of lipid emulsion on the elimination of phenytoin (Straathof et al. 1984) (14). Although the studies show some effect of lipid emulsion, this did not kindle more widespread interest in the subject. The serendipitous discovery of the apparently shielding effect of a large intravenous dose of lipid emulsion against bupivacaine toxicity in rats triggered renewed interest in the field (15). Additional experimental animal and isolated heart studies were performed (16-17), and although efficacy and safety had not been established by clinical trials, clinicians soon applied lipid therapy to seemingly hopeless cases of severe intoxication (18).

[0010] Intravenous lipid emulsion therapy for severe intoxication is a relatively young field. Although a few early studies on the pharmacokinetic effects of intravenous lipid emulsion exist (12-14; 20), its use as a treatment for severe intoxication was proposed as late as 1998 (15). Since this proposal, no randomized controlled human trials have been published. Thus, the evidence supporting this use of lipid emulsion consists only of animal studies and human case reports of varying quality (21).

[0011] Amyloid beta-peptide (Aβ) is a key molecule in Alzheimer disease (AD). Cerebral deposition of Aβ was earlier thought to initiate the pathological cascade of AD, including the formation of senile plaques and neurofibrillary tangles, neuronal loss, and dementia. According to the classical amyloid hypothesis, the aggregation of Aβ into insoluble β-sheet fibrils plays an important role in its neurotoxicity. However, this hypothesis is paradoxical: The concentrations of Aβ required for fibrillization and neurotoxicity are higher than its physiological concentrations. Cognitive decline in AD patients is not correlated with the levels of senile plaque formation or insoluble Aβ formation; instead it correlates with the levels of synapse loss and the levels of soluble Aβ. These observations suggest the existence of soluble toxic forms of Aβ in AD brains; these forms have recently been identified to be oligomeric assemblies of Aβ. At present, AD is believed to begin with synaptic dysfunction caused by soluble Aβ oligomers. This

hypothesis termed the oligomer hypothesis, is based on the following observations: The levels of Aβ oligomers are high in AD brains. Exogenous Aβ oligomers at physiological concentrations cause synaptic and cognitive dysfunction *in vivo* and synapse loss and neuronal death *in vitro*. Furthermore, it was observed that the E693delta mutation in the amyloid precursor protein found in AD patients causes disease by increasing the formation of Aβ oligomers without inducing the formation of Aβ fibrils or senile plaques. Currently, senile plaque formation is thought to occur in order to protect neurons from the toxicity of diffusible Aβ oligomers by sequestering them into deposits. Thus, soluble Aβ oligomers play a more important role in the etiology of AD insoluble Aβ fibrils (22).

[0012] The defining features of Alzheimer disease (AD) include conspicuous changes in both brain histology and behavior. The AD brain is characterized microscopically by the combined presence of 2 classes of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly insoluble, densely packed filaments. The soluble building blocks of these structures are amyloid-β (Aβ) peptides for plaques and tau for tangles. Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein, whereas tau is a brain-specific, axon-enriched microtubule-associated protein. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition. Synapse loss can be caused by the failure of live neurons to maintain functional axons and dendrites or by neuron death. During the past dozen years, a steadily accumulating body of evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytoplasmic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop. Because soluble toxic aggregates of both Aβ and tau can self-propagate and spread throughout the brain by prionlike mechanisms, successful therapeutic intervention for AD would benefit from detecting these species before plaques, tangles, and cognitive impairment become evident and from interfering with the destructive biochemical pathways that they initiate (23).

[0013] The increasing prevalence of Alzheimer's disease (AD) and a lack of effective prevention or disease-modifying therapies are global challenges with devastating personal, social

and economic consequences. The amyloid β (Aβ) hypothesis posits that cerebral β-amyloidosis is a critical early event in AD pathogenesis. However, failed clinical trials of Aβ-centric drug candidates have called this hypothesis into question. Whereas it is acknowledged that the Aβ hypothesis is far from disproven, the links between Aβ, tau and neurodegeneration are to be re-visited. The genetics, epidemiology and pathology of sporadic AD were reviewed and gave an updated account of what is currently known about the molecular pathogenesis of the disease (24).

[0014] The amyloid hypothesis has driven drug development strategies for Alzheimer's disease for over 20 years. A review about why accumulation of amyloid-β (Aβ) oligomers is generally considered causal for synaptic loss and neurodegeneration in AD was performed (25), presenting updated arguments for and against the amyloid hypothesis with new data and interpretations, and considering why the amyloid hypothesis may be failing therapeutically. Notably, several unresolved issues in the field including the presence of Aβ deposition in cognitively normal individuals, the weak correlation between plaque load and cognition, questions regarding the biochemical nature, presence and role of Aβ oligomeric assemblies *in vivo*, the bias of pre-clinical AD models toward the amyloid hypothesis and the poorly explained pathological heterogeneity and comorbidities associated with AD. It is also illustrated how extensive data cited in support of the amyloid hypothesis, including genetic links to disease, can be interpreted independently of a role for Aβ in AD. It was concluded that it is essential to expand the view of pathogenesis beyond Aβ and tau pathology and several future directions for AD research were suggested, which will be critical to understanding AD pathogenesis.

[0015] The aggregation and deposition of amyloid-β (Aβ) in the brain is thought to be an early event in the pathology of Alzheimer's disease (AD). Many studies have reported the association of Aβ with lipoproteins from plasma suggesting an involvement of lipoprotein particles in Aβ transport. Chylomicron-like lipid emulsions, resembling chylomicrons in composition, size and metabolism were prepared in the presence of [125I]$A\beta_{1-40}$. Aβ was found to associate significantly with these lipid emulsions during their preparation. The chylomicron-like emulsions containing Aβ were then injected into a lateral ear vein of conscious rabbits and blood sampled at regular intervals up to 30 mins. It was observed that there was no difference in the plasma clearance of [125I]Aβ and that of the 3H-cholesteryl ester, a marker of the emulsion particles, demonstrating that Aβ remains associated with these particles throughout both their lipolysis and tissue uptake. The results show that Aβ can be metabolized in association with triglyceride rich lipoproteins (TRLs). In addition the presence of specific markers of TRLs of

hepatic and intestinal origin in human CSF was reported, thus suggesting a potential means of cerebral Aβ delivery (26).

[0016] Docosahexaenoic acid (DHA), the main n-3 polyunsaturated fatty acid (PUFA) in membranes, is particularly abundant in brain cells. Decreased cerebral concentrations of DHA, resulting from dietary n-3 deficiency, are associated with impaired cognitive function. Because the cellular causes of this impairment are still unknown, we need *in vitro* models that mimic the variations in n-3/n-6 PUFA seen *in vivo*. PUFA profiles of hamster astrocytes cultured in medium supplemented were compared with long-chain PUFA [DHA and/or arachidonic acid (AA)] with those of brain tissue from hamsters fed an n-6/n-3 PUFA-balanced diet or one lacking n-3 PUFA. Astrocytes were obtained from the brain cortex of newborn hamsters and cultured in minimum essential medium + 5% fetal calf serum (FCS) supplemented with DHA and/or AA for 10 days. The astrocytes cultured in medium + FCS had low n-3 PUFA contents, comparable to those of brain tissue from hamsters fed an n-3-deficient diet. It was shown that astrocytes grown in medium supplemented with DHA and/or AA, plus alpha-tocopherol to prevent lipid peroxidation, incorporated large amounts of these long-chain PUFA, so that the n-6/n-3 PUFA compositions of the phosphatidylethanolamine and phosphatidylcholine, the two main classes of membrane phospholipids, were greatly altered. Astrocytes cultured in medium plus DHA had a more physiological n-3 status, grew better, and retained their astrocyte phenotype. Thus astrocytes in culture are likely to be physiologically relevant only when provided with adequate DHA. This reliable method of altering membrane phospholipid composition promises to be useful for studying the influence of n-6/n-3 imbalance on astrocyte function (27).

[0017] Rat neural stem cells/neural progenitors (NSC/NP) are generally grown in serum-free medium. NSC/NP were supplemented with the main long-chain polyunsaturated fatty acids (PUFAs) present in the brain, arachidonic acid (AA), or docosahexaenoic acid (DHA), and were monitored for their growth. Lipid and fatty acid contents of the cells were also determined. Under standard conditions, the cells were characterized by phospholipids displaying a highly saturated profile, and very low levels of PUFAs. When cultured in the presence of PUFAs, the cells easily incorporated them into the phospholipid fraction. The presence of three membrane proteins in the lipid raft fractions were also compared: GFR and connexin 43 contents in the rafts were increased by DHA supplementation, whereas Gbeta subunit content was not significantly modified. The restoration of DHA levels in the phospholipids could profoundly affect protein localization and, consequently, their functionalities (28).

[0018] Lipids are the fundamental structural components of biological membranes. For a long time considered as simple barriers segregating aqueous compartments, membranes are now viewed as dynamic interfaces providing a molecular environment favorable to the activity of membrane-associated proteins. Interestingly, variations in membrane lipid composition, whether quantitative or qualitative, play a crucial role in regulation of membrane protein functionalities. Indeed, a variety of alterations in brain lipid composition have been associated with the processes of normal and pathological aging. Although not establishing a direct cause-and-effect relationship between these complex modifications in cerebral membranes and the process of cognitive decline, evidence shows that alterations in membrane lipid composition affect important physicochemical properties notably impacting the lateral organization of membranes, and thus microdomains. It has been suggested that preservation of microdomain functionality may represent an effective strategy for preventing or decelerating neuronal dysfunction and cerebral vulnerability, processes that are both aggravated by aging. It was hypothesized that preservation of membrane organization, for example, through nutritional supplementation of docosahexaenoic acid, could prevent disturbances in and preserve effective cerebral function (29).

[0019] To date, no study has been performed to evaluate the antidotal effect of intravenous lipid emulsion on the poisoned patients' level of consciousness and routine metabolic profile tests in non-local anesthetic drug overdose. Taftachi *et al*. (30) aim was to evaluate the effect of intravenous intralipid administration as an antidote on the poisoned patients' Glasgow Coma Scale (GCS), hemodynamic parameters, arterial blood gas analysis, and routine metabolic profile tests (i.e., urea, glucose, sodium, and potassium) in the setting of non-local anesthetic drug overdose. In this randomized controlled trial, a total of 30 patients with non-local anesthetic drug intoxication were enrolled and randomly assigned into case (n=15) and control (n=15) groups. In the case group, all patients received 10 cc/kg intralipid 10% infusion. The patients in the control group just received the supportive care. Patients' demographic and clinical characteristics and results of their laboratory tests were evaluated at presentation and 6 hours after that. Mean age was 23 +/- 5 and 28 +/- 11 years in cases and controls, respectively. There were no significant statistical differences between these two groups regarding age, gender, elapsed time between intubation and extubation, and need for intubation and/or mechanical ventilation ($p = 0.70$ and $p = 1.00$, respectively). Also, systolic blood pressure, pulse rate, mean rate pressure product, respiratory rate, results of arterial blood gas analyses, serum sodium, potassium, urea, and creatinine on presentation and six hours later were not statistically significantly different

between the two study groups. However, a significant difference was found between the two groups in terms of GCS difference ($p = 0.048$) and blood glucose six hours after presentation ($p = 0.04$). In the setting of non-local anesthetic drug overdose, intravenous intralipid infusion can increase GCS and interestingly, decrease the blood glucose.

[0020] Lipid emulsions are widely used as carriers for hypnotics such as propofol, etomidate, and diazepam. It is assumed that the emulsions alone exert no effect on cellular functions nor influence the pharmacokinetics, pharmacodynamics, or anesthetic and analgetic potency of the hypnotics they carry. To elucidate possible interactions between lipid emulsions and cell membranes, in particular membrane-bound proteins, the effects of commercially available lipid emulsions on the cell membranes of cultured cortical neurons from the mouse was investigated by using the whole-cell configuration of the patch-clamp technique. Of nine lipid emulsions tested, three, i.e., Intralipid, Structolipid, and, to a much lesser extent, Abbolipid, activated membrane currents in the neuronal cells in a dilution-dependent manner. The emulsion-induced currents were not affected by picrotoxin or bicuculline but were inhibited by DL-AP5 and ketamine. The voltage dependence of the currents was influenced by the presence of Mg^{2+} in a way that is typical for currents conducted by N-methyl-D-aspartate receptor channels. It was concluded that Intralipid, Structolipid, and Abbolipid activate N-methyl-D-aspartate receptor channels in cortical neurons.

[0021] Lipid emulsions are widely used as carriers for hypnotics such as propofol, etomidate, or diazepam. We tested nine commercially available lipid emulsions and demonstrate that three of them--Intralipid, Structolipid, and Abbolipid-activate NMDA receptor channels in the membranes of cortical neuronal cells (31).

[0022] Haywood *et al*. (32) tested the hypothesis that lipids could act as an alternative fuel source in the brain during insulin-induced hypoglycemia. Male Sprague-Dawley rats were subjected to hyperinsulinemic (5 mU/kg/min) hypoglycemic (approximately 50 mg/dl) clamps. In protocol 1, intralipid (IL), a fat emulsion, was infused intravenously to prevent the fall in free fatty acid levels that occurs in response to hyperinsulinemic hypoglycemia. Intravenous lipid infusion did not alter the counterregulatory responses to hypoglycemia. To test whether IL could have central effects in mediating the counter regulatory response to hypoglycemia, in protocol 2 the brains of precannulated rats were intracerebroventricularly (icv) infused with IL or artificial cerebrospinal fluid (aCSF) as control. Unexpectedly, the epinephrine and glucagon response to hypoglycemia was significantly augmented with icv IL infusion. To determine whether central IL infusion could restore defective counter regulation, in protocol 3 rats were made recurrently

hypoglycemic (RH) for 3 days and on the 4th day underwent hyperinsulinemic hypoglycemic clamps with icv IL or aCSF infusion. RH rats had the expected impaired epinephrine response to hypoglycemia, and icv IL infusion again significantly augmented the epinephrine response in RH rats to normal. With regard to the experimental model of hypoglycemic counter regulation, it was concluded that 1) systemic lipid infusion did not alter the counter regulatory response to hypoglycemia, 2) the icv infusion of lipids markedly increased CSF FFA levels and paradoxically augmented the epinephrine and glucagon responses, and 3) the blunted sympathoadrenal response in recurrently hypoglycemic rats was completely normalized with the icv lipid infusion. It was concluded that, in the setting of insulin-induced hypoglycemia, increased brain lipids can enhance the sympathoadrenal response.

[0023] Lipid infusion reverses systemic local anesthetic toxicity. The acceptable upper limit for lipid administration is unknown and has direct bearing on clinical management. It was hypothesized that high volumes of lipid could have undesirable effects and sought to identify the dose required to kill 50% of the animals (LD(50)) of large volume lipid administration. Intravenous lines and electrocardiogram electrodes were placed in anesthetized, male Sprague-Dawley rats. Twenty percent lipid emulsion (20, 40, 60, or 80 mL/kg) or saline (60 or 80 mL/kg), were administered over 30 mins; lipid dosing was assigned by the Dixon "up-and-down" method. Rats were recovered and observed for 48 hrs then euthanized for histologic analysis of major organs. Three additional rats were administered 60 mL/kg lipid emulsion and euthanized at 1, 4, and 24 hrs to identify progression of organ damage. The maximum likelihood estimate for LD_{50} was 67.72 (SE, 10.69) mL/kg. Triglycerides were elevated immediately after infusion but returned to baseline by 48 hrs when laboratory abnormalities included elevated amylase, aspartate aminotransferase, and serum urea nitrogen for all lipid doses. Histologic diagnosis of myocardium, brain, pancreas, and kidneys was normal at all doses. Microscopic abnormalities in lung and liver were observed at 60 and 80 mL/kg; histopathology in the lung and liver was worse at 1 hr than at 4 and 24 hrs. The LD_{50} of rapid, high volume lipid infusion is an order of magnitude greater than doses typically used for lipid rescue in humans and supports the safety of lipid infusion at currently recommended doses for toxin-induced cardiac arrest. Lung and liver histopathology was observed at the highest infused volumes (33).

[0024] Intravenous lipid emulsion has been suggested as treatment for severe intoxications caused by lipophilic drugs, including tricyclic antidepressants. The effect of lipid infusion on plasma and tissue concentrations of amitriptyline and haemodynamic recovery was investigated, when lipid was given after amitriptyline distribution into well-perfused organs. Twenty

anaesthetized pigs received amitriptyline intravenously 10 mg/kg for 15 min. Thirty minutes later, in random fashion, 20% Intralipid(®) (Lipid group) or Ringer's acetate (Control group) was infused 1.5 ml/kg for 1 min. followed by 0.25 ml/kg/min. for 29 min. Arterial and venous plasma amitriptyline concentrations and haemodynamics were followed till 75 min. after amitriptyline infusion. Then, frontal brain and heart apex samples were taken for amitriptyline measurements. Arterial plasma total amitriptyline concentrations were higher in the Lipid than in the Control group ($p < 0.03$) from 20 min. on after the start of the treatment infusions. Lipid emulsion reduced brain amitriptyline concentration by 25% ($p = 0.038$) and amitriptyline concentration ratios brain/arterial plasma ($p = 0.016$) and heart/arterial plasma ($p = 0.011$). There were no differences in ECG parameters and no severe cardiac arrhythmias occurred. Two pigs developed severe hypotension during the lipid infusion and were given adrenaline. In conclusion, lipid infusion, given not earlier than after an initial amitriptyline tissue distribution, was able to entrap amitriptyline back into plasma from brain and possibly from other highly perfused, lipid-rich tissues. In spite of the entrapment, there was no difference in haemodynamics between the groups (34).

[0025] Malathion is one of the most widely used organophosphate pesticides and herbicides. It has given rise to major clinical problems by its poisoning in all over the world. Malathion also a highly lipophilic agent, and tends to accumulate within lipid-rich tissue like a brain in the body, causing toxicity. Therefore, it was investigated if there is a possible beneficial effect of using intralipid fat emulsion (IFE) on the neurotoxicity, and to detect it time-dependently at the beginning, 6^{th} and 12^{th} hours of M intoxication. Forty-eight rats were randomly divided into six groups including: control (C), Lipid (L) group (18.6 mL/kg oral IFE), Malathion (M) group (10 mg/kg oral M), M0L group (IFE treated after immediate from M), M6L group (IFE treated after 6 hours from M), M12L group (IFE treated after 12 hours from M). M group in comparison with all others group, there was an increase in the total oxidant status (TOS) level. M group in comparison with C, L, M0L groups, it was seen significantly decrease in the total antioxidant capacity (TAC) level. Interestingly, M group in comparison with M6L and M12L groups, there was no significant difference among these groups in terms of the TAC levels. Although there was no significant difference among C, L and M0L groups in terms of both TAC and TOS levels, but was significant difference C, L groups in comparison with M6L, M12L groups in terms of TAC levels. C group in comparison with L, M0L, M6L, M12L groups in terms of TOS levels, there was no significant difference. These findings have indicated that IFE seriously reduced TOS levels in all the groups depending on time. Also, M0L group in comparison with

M6L and M12L groups, there was significantly increase of the TAC levels. There was no statistically significant difference between M6L and M12L groups. These biochemical results were confirmed with immunohistochemical results. The study has had some certain evidence that IFE is a promising safe therapy for acutely intoxicated cases by organophosphate. It is much more effective if used at the beginning of organophosphate poisoning. As such, there is no need to avoid using IFE in clinical practice (35).

[0026] Chlorpyriphos is one of the most widely used organophosphate (OP) insecticide in agriculture with potential toxicity. Current post-exposure treatments consist of anti-cholinergic drugs and oxime compounds. The effects of intralipid and caffeic acid phenethyl ester (CAPE) on chlorpyriphos toxicity was studied to compose an alternative or supportive treatment for OP poisoning. Forty-nine rats were randomly divided into seven groups. Chlorpyriphos was administered for toxicity. Intralipid (IL) and CAPE administered immediately after chlorpyriphos. Serum acetylcholinesterase (AChE) level, total oxidant status (TOS), total antioxidant response (TAR), and histologic examination of cerebellum and brain tissue with Hematoxylin-Eosin and immunohistochemical dyes were examined. Serum enzym levels showed that chlorpyriphos and CAPE inhibited AChE while IL alone had no effect, chlorpyriphos and CAPE intensifies the inhibition effect. Significant difference at AChE levels between the chlorpyriphos+IL and chlorpyriphos+CAPE verified that IL has a protective effect on AChE inhibition. TAR levels were significantly increased in all groups except chlorpyriphos group, TOS levels revealed that CAPE and IL decrease the amount of oxidative stress. Histologic examination revealed that neuronal degeneration was slightly decreased at chlorpyriphos+IL group, but CAPE had a significant effect on protection of neuronal degeneration. The results gave three key points. 1) AChE activity is important for diagnosis of OP intoxication but it has no value for determining the neuro-degeneration. 2) CAPE inhibits AChE activity and may increase the muscarinic-nicotinic hyperactivation. Therefore it should not be used for treatment of OP intoxication. 3) IL decreases the severity of neurodegeneration and symptoms of OP intoxication and it can be used as a supportive agent (36).

[0027] Intravenous lipid emulsion has been suggested as treatment for local anaesthetic toxicity, but the exact mechanism of action is still uncertain. Controlled studies on the effect of lipid emulsion on toxic doses of local anaesthetics have not been performed in man. In randomized, subject-blinded and two-phase cross-over fashion, eight healthy volunteers were given a 1.5 ml/kg bolus of 20% Intralipid(®) (200 mg/ml) or Ringer's acetate solution intravenously, followed by a rapid injection of lidocaine 1.0 mg/kg. Then, the same solution as in

the bolus was infused at a rate of 0.25 ml/kg/min. for 30 min. Electroencephalography (EEG) was recorded, and 5 min. after lidocaine injection, the volunteers were asked to report subjective symptoms. Total and un-entrapped lidocaine plasma concentrations were measured from venous blood samples. EEG band power changes (delta, alpha and beta) after the lidocaine bolus were similar during lipid and during Ringer infusion. There were no differences between infusions in the subjective symptoms of central nervous system toxicity. Lidocaine was only minimally entrapped in the plasma by lipid emulsion, but the mean un-entrapped lidocaine area under concentration-time curve from 0 to 30 min. was clearly smaller during lipid than Ringer infusion (16.4 versus 21.3 mg × min/l, p = 0.044). Intravenous lipid emulsion did not influence subjective toxicity symptoms nor affect the EEG changes caused by lidocaine (37).

Intralipid treatment for Alzheimer Disease

[0028] Lange *et al*. (38) described a case of severe central nervous system toxicity after an overdose of lidocaine by local infiltration in a peritoneal dialysis patient and subsequent treatment of the toxicity with lipid emulsion. A 31-year-old male received an iatrogenic overdose of 1600 mg of lidocaine 2% by infiltration during an attempt to remove and replace a peritoneal dialysis catheter. Within 10 minutes after the last lidocaine injection, the patient exhibited features of local anesthetic toxicity, which included tachycardia, hypertension, shortness of breath, dizziness, and a choking sensation that progressed to hallucinations, dysarthria, and uncoordinated, weak limb movement. Within 10 minutes after administration of a single 1.5-mg/kg intravenous bolus of 1.5 mL/kg [corrected], the patient improved dramatically. After observation overnight in a monitored care setting, the patient was discharged home with no apparent neurologic sequelae.

[0029] Systemic toxicity due to regional anesthesia with local anesthetic agents such as lidocaine has been well described in the medical literature. The use of lipid emulsion as an antidote to the toxicity of local anesthetics and other lipophilic drugs has been suggested as a valuable intervention in both early, rapidly progressive toxicity, as well as toxicity that is refractory to standard treatment. Patients with advanced chronic kidney disease may be more susceptible to systemic effects of lidocaine due to decreased drug elimination. Central nervous system toxicity due to an overdose of lidocaine was quickly reversed by intravenous lipid emulsion in the patient (38).

[0030] The major component fatty acids in Intralipid are linoleic acid (44-62%), oleic acid (19-30%), palmitic acid (7-14%), a-linolenic acid (4-11%) and stearic acid (1.4-5.5%) (39).

[0031] Oxidative stress is a hallmark of many degenerative disorders. The brain is particularly vulnerable to this phenomenon owing to high oxygen consumption, enrichment in polyunsaturated fatty acids (PUFAs) and high levels in redox metal ions (40). Lipid peroxidation products (LPPs) have been found in brain, cerebrospinal fluid and plasma from patients with Alzheimer's disease (AD) (40). Primary substrates for lipid peroxidation are PUFAs and include ω-6 fatty acids (for example, linoleic acid and arachidonic acid) as well as ω-3 fatty acids (for example, docosahexaenoic acid). Reactive oxygen species are responsible for starting the chain by the production of an unstable lipid radical that is converted to a lipid peroxyl radical, leading to the peroxidation of other fatty acids (propagation). This chain reaction stops (termination) when two radicals react to produce a non-radical species, or as a result of antioxidants (for example, vitamin C and vitamin E) and enzymes of the superoxide dismutase, catalase and peroxidase families (40). Oxidized PUFAs are further degraded to toxic products, such as 4-hydroxy-2-nonenal (HNE), acrolein and other short-chain aldehydes. Importantly, amyloid-β has been shown to cause oxidative stress through its interaction with transition metal ions, such as Cu^{2+} and Zn^{2+}, which are enriched in senile plaques (40). Amyloid-β can reduce these metal ions, thus producing hydrogen peroxide. During this process, amyloid-β becomes oxidized, thereby leading to the crosslinking of some of its residues' side-chains and the formation of aggregate-prone adducts. Alternatively, hydrogen peroxide can be generated catalytically from Cu^{2+}- or Zn^{2+}-bound amyloid-β using other electron donors (for example, PUFAs and cholesterol), a process leading to the generation of toxic LPPs, such as oxysterol and HNE. Finally, amyloid-β itself can be crosslinked by HNE. Key challenges in the field are to understand the role of LPP accumulation in the progression of AD-associated manifestations.

[0032] The linoleic acid metabolism was examined in the brain cortex of 4 month-old and 24 month-old rats. After the injection of [1-14C]-linoleate into the lateral ventricle of the brain the animals were sacrificed at 1, 3 and 6 hours from the injection. The linoleate (18:2) incorporation into lipids, the presence of fatty acid peroxidation products, as well as the 18:2 transformation into elongated and desaturated derivatives were determined. Both an age-related reduction in linoleate incorporation rate into glycerophospholipids and a decrease in fatty acid turnover were found. Furthermore, in glycerophospholipids from 24 month-old rat brain cortex a higher level of hydroperoxide derivative of linoleate was found as compared to 4 month-old animals, and this damaged fatty acid is eliminated more slowly in aged rats than in adults. Finally, unlike 4 month-old animals, a stimulation of the transformation rate of linoleate into desaturation (6,9,12-C18:3) and elongation (8,11,14,C20:3) products was found in 24 month-old rat brain cortex. On the

contrary, as far as arachidonic acid (one of the most important end products of the mechanism of linoleate modification) is concerned, the differences between aged and control animals were small, making it quite difficult to attribute a physiological meaning to this phenomenon (41).

[0033] Alzheimer's disease and associated diseases constitute a major public health concern worldwide. Nutrition-based, preventive strategies could possibly be effective in delaying the occurrence of these diseases and lower their prevalence. Arachidonic acid is the second major polyunsaturated fatty acid (PUFA) and several studies support its involvement in Alzheimer's disease. How dietary arachidonic acid contributes to Alzheimer's disease mechanisms was examined and used to assess prevention thereof. The sources of neuronal arachidonic acid that could potentially originate from either the conversion of linoleic acid, or from dietary sources and transfer across the blood-brain-barrier, was explored. Then, a brief overview of the role of the two main agents of Alzheimer's disease, tau protein and Aβ peptide was conducted, followed by the examination of the relationship between arachidonic acid and the disease. Finally, the putative mechanisms by which arachidonic acid could influence Alzheimer's disease occurrence and evolution were concluded. The conclusion was devoted to what remains to be determined before integrating arachidonic acid in the design of preventive strategies against Alzheimer's disease and other neurodegenerative diseases (42).

[0034] Insulin resistance and type 2 diabetes are associated with an increased risk of neurodegenerative diseases. Brain-derived neurotrophic factor (BDNF) regulates neuronal differentiation and synaptic plasticity, and its decreased levels are supposed to play a role in the pathogenesis of Alzheimer's disease and other disorders. The effects of hyperinsulinemia and serum free fatty acids (FFA) elevation on circulating BDNF concentration in humans was estimated. 18 healthy male subjects were studied (mean age 25.6 ± 3.0 years; mean BMI 26.6 ± 4.8 kg/m^2). Serum and plasma BDNF concentration was measured in the baseline state and in the 120 and 360 min of euglycemic hyperinsulinemic clamp with or without intralipid/heparin infusion. Furthermore, plasma BDNF was measured in 20 male subjects (mean age 22.7 ± 2.3 years; mean BMI 24.9 ± 1.5 kg/m^2) 360 min after a highfat meal. Insulin sensitivity was reduced by ~40% after 6 h of intralipid/heparin infusion ($P < 0.001$). During both clamps, serum and plasma BDNF followed the same pattern. Hyperinsulinemia had no effect on circulating BDNF. Raising FFA had no effect on circulating BDNF in 120 min; however, it resulted in a significant decrease by 43% in serum and by 35% in plasma BDNF after 360 min ($P = 0.005$ and 0.006, respectively). High-fat meal also resulted in a decrease by 27.8% in plasma BDNF ($P = 0.04$).

The data showed that raising FFA decreases circulating BDNF. This might indicate a potential link between FFA-induced insulin resistance and neurodegenerative disorders (43).

[0035] Rodriguez-Navas *et al*. (44) analyzed the fatty acid profile of brains and plasma from male and female mice fed chow or a western-style high fat diet (WD) for 16 weeks to determine if males and females process fatty acids differently. Based on the differences in fatty acids observed *in vivo*, we performed *in vitro* experiments on N43 hypothalamic neuronal cells to begin to elucidate how the fatty acid milieu may impact brain inflammation. Using a comprehensive mass spectrometry fatty acid analysis, which includes a profile for 52 different fatty acid isomers, the plasma and brain fatty acid composition of age-matched male and female mice maintained on chow or a WD were assayed. Additionally, using the same techniques, the fatty acid composition of N43 hypothalamic cells following exposure to palmitic and linoleic acid, alone or in combination, were determined. The data demonstrated there is a sexual dimorphism in brain fatty acid content both following the consumption of the chow diet, as well as the WD, with males having an increased percentage of saturated fatty acids and reductions in ω6-polyunsaturated fatty acids when compared to females. Interestingly, no sexual dimorphism in fatty acid content in the plasma of the same mice was observed. Furthermore, exposure of N43 cells to the ω6-PUFA linoleic acid, which is higher in female brains when compared to males, reduces palmitic acid-induced inflammation. The data suggested male and female brains, and not plasma, differ in their fatty acid profile. This was the first time lipidomic analyses has been used to directly test the hypothesis there is a sexual dimorphism in brain and plasma fatty acid composition following consumption of the chow diet, as well as following exposure to the WD.

Blood-brain barrier

[0036] Treatment strategies for Alzheimer's disease (AD) are still elusive. Thus, new strategies are needed to understand the pathogenesis of AD in order to provide suitable therapeutic measures. Available evidences suggest that in AD, passage across the blood-brain barrier (BBB) and transport exchanges for amyloid-β-peptide (ABP) between blood and the central nervous system (CNS) compartments play an important regulatory role for the deposition of brain ABP. New evidences suggest that BBB is altered in AD. Studies favoring transport theory clearly show that ABP putative receptors at the BBB control the level of soluble isoform of ABP in brain. This is achieved by regulating influx of circulating ABP into brain via specific receptor for advanced glycation end products (RAGE) and gp330/megalin-mediated transcytosis. On the other hand, the efflux of brain-derived ABP into the circulation across the vascular

system via BBB is accomplished by low-density receptor-related protein-1 (LRP1). Furthermore, an increased BBB permeability in AD is also likely since structural damage of endothelial cells is quite frequent in AD brain. Thus, enhanced drug delivery in AD is needed to induce neuroprotection and therapeutic success. For this purpose, nanodrug delivery could be one of the available options that require active consideration for novel therapeutic strategies to treat AD cases. Sharma *et al*. (45) focused on these aspects and provides new data showing that BBB plays an important role in AD-induced neurodegeneration and neurorepair.

[0037] The BBB is a tightly regulated barrier in the central nervous system. Though the BBB is thought to be intact during neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD), recent evidence argues otherwise. Dysfunction of the BBB may be involved in disease progression, eliciting of peripheral immune response, and, most importantly, altered drug efficacy. Desai *et al*. (44) gives a brief overview of the BBB, its components, and their functions. It evaluated the current literature in AD and PD BBB pathology resulting from insult, neuroinflammation, and neurodegeneration, and specifically discussed alterations in tight junction, transport and endothelial cell surface proteins, and vascular density changes, all of which result in altered permeability. Finally, Desai *et al*. discussed the implications of BBB dysfunction in current and future therapeutics. Developing a better appreciation of BBB dysfunction in AD and PD may not only provide novel strategies in treatment, but will prove an interesting milestone in understanding neurodegenerative disease etiology and progression.

[0038] It is not clear whether Alzheimer's Disease (AD) is primarily a neurodegenerative disorder or not. A body of evidence suggests that vascular disorder in brains of individuals with AD contributes to the extremes of this disease. This raises a question whether Alzheimer's dementia is secondary to vascular dysfunction in the central nervous system (CNS) and, therefore, the neurodegeneration that follows is a consequence of inadequate cerebral blood flow, altered brain metabolism and failure in physiological functions of brain endothelium which represents a site at the BBB. The evidence for a primary role of the CNS vascular system in pathogenesis of Alzheimer's dementia was reviewed to show how alterations in transport across the BBB contribute to development of cerebral beta-amyloidosis in AD. In addition, vascularly-based therapeutic strategies to limit the development of beta-amyloidosis and to remove amyloid and plaques from the CNS of AD individuals were also discussed (47).

[0039] Protection of the brain is strengthened by active transport and ABC transporters. P-glycoprotein (P-gp) at the BBB functions as an active efflux pump by extruding a substrate from the brain, which is important for maintaining loco-regional homeostasis in the brain and

protection against toxic compounds. Importantly, dysfunctional BBB P-gp transport is postulated as an important factor contributing to accumulation of aggregated protein in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Furthermore, P-gp is a major factor in mediating resistance to brain entry of numerous exogenous compounds, including toxins that can be involved in PD pathogenesis. Bartels (48) highlights the role of altered P-gp function in the pathogenesis and progression of neurodegenerative disease. And further discusses the implications of alterations in P-gp function for the treatment of these diseases.

[0040] Although intravenous lipid emulsion (ILE) was first used to treat life-threatening local anesthetic (LA) toxicity, its use has expanded to include both non-local anesthetic (non-LA) poisoning and less severe manifestations of toxicity. A collaborative workgroup appraised the literature and provides evidence-based recommendations for the use of ILE in poisoning. Following a systematic review of the literature, data were summarized in four publications: LA and non-LA poisoning efficacy, adverse effects, and analytical interferences. Twenty-two toxins or toxin categories and three clinical situations were selected for voting. Voting statements were proposed using a predetermined format. A two-round modified Delphi method was used to reach consensus on the voting statements. Disagreement was quantified using RAND/UCLA Appropriateness Method. For the management of cardiac arrest, using ILE with bupivacaine toxicity was recommended, while recommendations are neutral regarding its use for all other toxins. For the management of life-threatening toxicity: (1) as first line therapy, it was suggested not to use ILE with toxicity from amitriptyline, non-lipid soluble beta receptor antagonists, bupropion, calcium channel blockers, cocaine, diphenhydramine, lamotrigine, malathion but are neutral for other toxins; (2) as part of treatment modalities, it was suggested using ILE in bupivacaine toxicity if other therapies fail, but are neutral for other toxins; (3) if other therapies fail, it was recommended using ILE for bupivacaine toxicity and using ILE for toxicity due to other LAs, amitriptyline, and bupropion, but recommendations are neutral for all other toxins. In the treatment of non-life-threatening toxicity, recommendations are variable according to the balance of expected risks and benefits for each toxin. For LA-toxicity the use of Intralipid® 20% was suggested. There is no evidence to support a recommendation for the best formulation of ILE for non-LAs. The voting panel is neutral regarding ILE dosing and infusion duration due to insufficient data for non-LAs. All recommendations were based on very low quality of evidence.

[0041] Clinical recommendations regarding the use of ILE in poisoning were only possible in a small number of scenarios and were based mainly on very low quality of evidence, balance of expected risks and benefits, adverse effects, laboratory interferences as well as related costs

and resources. The workgroup emphasizes that dose-finding and controlled studies reflecting human poisoning scenarios are required to advance knowledge of limitations, indications, adverse effects, effectiveness, and best regimen for ILE treatment (49).

[0042] Intralipid emulsion therapy is well-established for the treatment of local-anesthetic systemic toxicities. In recent years, its role has expanded as an important therapeutic agent in the reversal of other types of drug overdoses, including certain types of antipsychotics, antidepressants, antiarrhythmics, and calcium channel blockers. A literature review identified thirty-one case reports including forty-nine separate drug overdose cases involving ten separate drug classes which were successfully reversed with Intralipid. Muller *et al*. (50) describes an elderly unresponsive woman refractory to conventional treatments after ingesting a potentially lethal amount of 5.6 grams of diltiazem in a suicide attempt. After treatment with Intralipid over a twenty-four hour period, the patient's hemodynamic and metabolic derangements were corrected and stabilized completely. Intralipid emulsion rescue therapy provides another potential strategy for the reversal of many drug toxicities, most likely by providing a lipid layer safety net for drug overdose by passive diffusion. Clinicians are urged to embrace an expanded role of Intralipid emulsion rescue therapy, not only for local anesthetic drug toxicities, but also for other lipophilic drug overdoses.

[0043] Caffeine is arguably the most widely used stimulant drug in the world. Muraro *et al*. (51) describes a suicide attempt involving caffeine overdose whereby the patient's severe intoxication was successfully treated with the prompt infusion of Intralipid. A 19-year-old man was found in an agitated state at home by the volunteer emergency team about 1 h after the intentional ingestion of 40 g of caffeine (tablets). His consciousness decreased rapidly, followed quickly by seizures, and electrocardiographic monitoring showed ventricular fibrillation. Advanced life support maneuvers were started immediately, with the patient defibrillated 10 times and administered 5 mg epinephrine in total and 300 + 150 mg of amiodarone (as well as lidocaine and magnesium sulfate). The cardiac rhythm eventually evolved to asystole, necessitating the intravenous injection of epinephrine to achieve the return of spontaneous circulation. However, critical hemodynamic instability persisted, with the patient's cardiac rhythm alternating between refractory irregular narrow complex tachycardia and wide complex tachycardia associated with hypotension. In an attempt to restore stability three successive doses of Intralipid (120 + 250 + 100 mg) were administered, which successfully prevented a severe cardiovascular collapse due to a supra-lethal plasma caffeine level (>120 mg/L after lipid emulsion). The patient survived without any neurologic complications and was transferred to a

psychiatric ward a few days later. The case emphasizes the efficacy of intravenous lipid emulsion in the resuscitation of patients from non-local anesthetic systemic toxicity. Intralipid appears to act initially as a vehicle that carries the stimulant drug away from heart and brain to less well-perfused organs (scavenging mechanism) and then, with a sufficient drop in the caffeine concentration, possibly as a tonic to the depressed heart.

[0044] Thrombosis and immune dysfunction are two important complications that result from the administration of parenteral nutrition. Endothelial cells within the vasculature are crucial components necessary for maintenance of normal coagulation and immune function.

[0045] The effects of three commercial lipid emulsions (LEs; Intralipid®, ClinOleic® [or Clinolipid®], and Omegaven®) differing in the levels of omega-6 polyunsaturated fatty acids, omega-3 polyunsaturated fatty acids, omega-9 monounsaturated fatty acids, and saturated fatty acids upon endothelial cell fatty acid composition using Gas chromatography, endothelial cell integrity, were compared by assessing measurement of apoptosis and necrosis using flow cytometry, endothelial cell inflammatory activation by assessing the induction of ICAM-1 by lipopolysaccharide [LPS]), and transcription factor activation (phosphorylation of NF-κB) using western blot analysis. Gas chromatographic analysis confirmed cellular uptake of the fatty acids within the LEs; furthermore, these fatty acid changes reflected the composition of the oils and egg phosphatides used in the manufacturing of these emulsions. However, the kinetics of fatty acid uptake and processing differed between LEs. Fish oil LE negatively impacted cell viability by doubling the percentage of apoptotic and necrotic cell populations quantified by flow cytometry using Annexin V/Fluorescein and propidium iodide. The soybean oil LE did not alter cell viability, while the olive oil-predominate emulsion improved cell viability. All LEs were capable of suppressing LPS-induced ICAM-1 expression; however, the fish oil LE was more potent than the other emulsions. Fish oil LE supplementation of cells also suppressed LPS-induced phosphorylation of NF-κB, while the soybean oil and olive predominant LE had no effect upon NF-κB phosphorylation. Lipid emulsions are readily incorporated and stored in the form of triacylglycerols. Soybean oil-based, olive oil-predominant and fish-oil based LEs differentially affected endothelial cell integrity. Importantly, these three LEs were capable of suppressing endothelial cell inflammatory response despite their fatty acid content (52).

[0046] Membrane currents conducted by the NMDA receptor channels were investigated in cultured cortical neurons and TsA cells transfected with NR1-1a/NR2A subunits of the NMDA receptor. The whole-cell recording technique was used. Current transients evoked by bath application of NMDA for 5 s were characterized by a fast peak and a slow decay to 46.1 +/-

15.5% of the peak level at the end. When NMDA was applied in combination with various lipid emulsions (Intralipid, ClinOleic, Lipofundin or Abbolipid, the NMDA induced currents were reduced, although this reduction did not affect the fast peak, it did affect the decay phase. The amount of reduction depended on the concentration of the lipids (in the case of Abbolipid diluted at 1:40, the current at the end of the 5-s drug application was approximately 2/3 of control). When Abbolipid was applied 40 s before NMDA, peak and late current were reduced to approximately 2/3. The effect of current reduction was the same at either of the two chosen membrane potentials (-80 and +40 mV) which indicates that the effect was not mediated by contamination of the emulsions with Mg^{2+}. The current reduction produced by Abbolipid was about the same in native neuronal cells and in TsA cells expressing the NR1-1a/NR2A subunits. The current reducing effect of the lipid emulsions may add to the anesthetic, analgesic and neuroprotective effects seen with hypnotics administered by way of lipid carriers (53).

[0047] Little is known about the impact of circulating lipids on brain processes. Building on evidence that chronic fat consumption stimulates hypothalamic peptides in close association with elevated triglycerides (TG), this study examined whether an acute rise in TG levels induced by fat emulsion can affect these hypothalamic systems. In normal weight rats, ip injection of Intralipid (20%, 5 ml) during the first 4 h after injection produced a robust increase in TG levels and non-esterified fatty acids, but had no impact on glucose, insulin, or leptin levels. This was accompanied by a marked increase in the expression of particular orexigenic peptides, galanin, orexins, and the opioid, enkephalin, which are known to be positively related to fat ingestion. This effect, similarly induced by 4 h of high fat diet consumption, was detected in the paraventricular nucleus (PVN) for galanin, in the perifornical hypothalamus (PFH) for orexins, and in the PVN, PFH, as well as the arcuate nucleus (ARC) for enkephalin. It was not seen, however, for neuropeptide Y and agouti-related protein localized in the ARC, which are unaffected or reduced by dietary fat. This site specificity was confirmed by c-Fos immunostaining, a marker of neuronal activity, which was increased by Intralipid in the PVN and PFH, but not in the ARC, and was detected in 20% of orexin-expressing neurons in the PFH. These findings suggest that circulating lipids, through different mechanisms, may stimulate hypothalamic neurons, which synthesize specific feeding stimulatory peptides that possibly contribute to hyperphagia during consumption of a fat-rich diet (54).

Conclusions

[0048] Intralipid treatment is first suggested here for the treatment of Alzheimer disease. It should be given intravenously on a monthly basis according to each patient's response. Clinical studies should be done in order to evaluate this new treatment modality.

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SUMMARY OF THE INVENTION

[0049] Postoperative delirium (POD) is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. The present invention is the first to suggest a new treatment for POD by intravenous intralipid injection in the recovery room when POD is determined.

DETAILED DESCRIPTION OF THE INVENTION

Intralipid for Treating Post Operative Delirium

[0050] Delirium is defined by either the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) (1) or by the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD 10, Table 3) (2). Delirium is an acute and fluctuating alteration of mental state of reduced awareness and disturbance of attention. POD (Post Operative Delirium) often starts in the recovery room and occurs up to 5 days after surgery (3-5). One investigation (4) found that many patients with POD on the peripheral ward already had POD in the recovery room.

[0051] More than 230 million surgical procedures are performed each year worldwide, of which more than 80 million are in Europe (6-8). In Europe, the in-hospital mortality rate up to a maximum of 60 days is 3% after elective surgery and nearly 10% after emergency surgery (7). In addition to mortality, postoperative cognitive impairments such as POD and postoperative cognitive dysfunction (POCD) impose a huge burden on individuals and society (9). The incidence of POD is dependent on perioperative and intraoperative risk factors (10). Therefore, the incidence of POD varies within a broad range (11, 12). For example, a meta-analysis of 26 studies of POD reported an incidence of 4.0 to 53.3% in hip fracture patients and 3.6 to 28.3% in elective patients (13).

[0052] Delirium is one of the most common complications following hip fracture surgery in older people. Pre- and peri-operative factors associated with the development of post-operative delirium following hip fracture surgery were identified.

[0053] Published and unpublished literature were searched to identify all evidence reporting variables on patient characteristics, on-admission, intra-operative and post-operative management assessing incident delirium in older people following hip fracture surgery. Pooled odds ratio (OR) and mean difference of those who experienced delirium compared to those who did not were calculated for each variable. Evidence was assessed using the Downs and Black appraisal tool and interpreted using the GRADE approach. A total of 6704 people (2090 people

with post-operative delirium) from 32 studies were analysed. There was moderate evidence of nearly a two-times greater probability of post-operativedelirium for those aged 80 years and over (OR: 1.77; 95% CI: 1.09, 2.87), whether patients lived in a care institution pre-admission (OR: 2.65; 95% CI: 1.79, 3.92), and a six-times greater probability of developing post-operative delirium with a pre-admission diagnosis of dementia (OR: 6.07, 95% CI: 4.84, 7.62). There was no association with intra-operative variables and probability of delirium. Clinicians treating people with a hip fracture should be vigilant towards post-operative delirium if their patients are older, have pre-existing cognitive impairment and poorer overall general health. This is also the case for those who experience post-operative complications such as pneumonia or a urinary tract infection (14).

[0054] Post-operative cerebral dysfunction includes delirium, usually occurring early and reversible, and post-operative cognitive disorders, usually occurring later and prolonged. This is a frequent complication in patients older than 75 years old. The two neurological pictures are often inter-related. The pathophysiology of both entities is similar and related to post-operative neuro-inflammation; therefore onset may occur independently of any surgical complication. Post-operative cerebral dysfunction is a serious organic complication. Reduction of inflammation represents the most logical preventive measure but currently there are no studies that show this to be effective. Prevention therefore means combining several minor measures, elements that fit well into programs of enhanced post-operative recovery after surgery. Diminished pre-operative cognitive status being a major risk factor, pre-operative rehabilitation combining nutritional, physical and cognitive support can be helpful (15).

[0055] Postoperative delirium is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. It is of great importance to identify patients at risk for delirium, in order to focus preventive strategies. Raats *et al*. (16) systematically reviewed current available literature on pre-operative risk factors for delirium after vascular surgery. A systematic literature search was conducted using PubMed and EMBASE, using the MeSH terms and key words "delirium", "surgery" and "risk factor". Studies were retained for review after meeting strict inclusion criteria that included only prospective studies evaluating risk factors for delirium in patients who had elective vascular surgery. Diagnosis of delirium needed to be confirmed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD-10. Fifteen articles were selected for inclusion, incidence of delirium across the studies ranged from 5% to 39%. Many factors have been associated with increased risk of delirium, including age, cognitive impairment, comorbidity, depression,

smoking, alcohol, visual and hearing impairment, ASA-score, biochemical abnormalities, operative strategies and blood loss. Delirium is a common complication after elective vascular surgery in elderly. The highest delirium incidence was observed after open aortic surgery as well as after surgery for critical limb ischemia. A picture starts to form of which predisposing factors lead to increased risk of delirium. The leading risk factors consistently identified in this systematic review were advanced age and cognitive impairment. Multi-disciplinary specialist-led interventions in the preoperative phase could decrease incidence and severity of delirium and should be focused on identified high-risk patients.

[0056] Ruggiero *et al*. (17) investigates the relationship between cognitive dysfunction or delirium detected in the early post-surgical phase and the 1-year mortality among 514 hip fracture hospitalized older persons. Patients with early cognitive dysfunction or delirium experienced a 2-fold increased mortality risk. Early post-operative cognitive dysfunction and delirium are negative prognostic factors for mortality. Premorbid cognitive impairment and dementia in older individuals negatively affect functional recovery after hip fracture. Additionally, post-operative delirium is an established risk factor for negative outcomes among hip fracture patients. While the majority of hip fracture patients experience minor post-surgical cognitive dysfunction, the prognostic value of this phenomenon is unknown. Therefore, the relationship between minor cognitive dysfunction or delirium detected in the early post-surgical phase and the 1-year mortality after index hip fracture were investigated.

[0057] 514 patients with hip fracture (77.4 % women), aged 65 years or older (mean age 83.1 ± 7.3 years), who underwent surgical hip fracture repair, were enrolled. Patients were assessed daily from the second to the fourth post-operative day and at 3, 6, and 12 months thereafter. All participants underwent comprehensive assessment, including detection of delirium by using the confusion assessment method and evaluation of cognitive function by using mini-mental state examination (MMSE; score range 0 to 30, with lower scores indicating poorer performance). In the absence of delirium, post-surgical cognitive dysfunction was defined as having low performance on MMSE. Vital status of 1 year after the index fracture and date of death were gathered from local registries. The observed 1-year mortality rate was 14.8 %. Men were more likely to die than women within 1 year of the index fracture ($p < 0.01$). Compared to participants with better cognitive performance, those with MMSE < 24, as well as those with delirium in the post-operative phase, showed a significantly higher 1-year mortality rate (23.3 versus 17.9 and 8.1 %, respectively). Independent of age and sex, post-operative cognitive dysfunction as well as delirium was both associated with a 2-fold increased mortality risk. The

presence of minor cognitive dysfunction in the early post-surgical phase is a negative prognostic factor for mortality among elderly hip fracture patients. The burden of minor cognitive dysfunction is likely superimposed on that of delirium in subgroups of frail patients.

[0058] Perioperative cerebral hypoperfusion/ischemia is a major inciting factor of post-operative delirium, which is coupled with adverse outcome in elderly patients. Cerebral oximetry enables noninvasive assessment of the regional cerebral oxygen saturation (rSO_2). Various investigations whether perioperative rSO_2 variations were linked to delirium in elderly patients after spinal surgery were conducted. Postoperative delirium was assessed for 48 hours postsurgery in 109 patients aged over 60 years without a prior history of cerebrovascular or psychiatric diseases by the Confusion Assessment Method for the intensive care unit and the intensive care delirium screening checklist. The rSO_2 values immediately before and throughout surgery were acquired. The preoperative cognitive functions, patient characteristics, and perioperative data were recorded. During the 48-h postoperative period, 9 patients (8%) exhibited delirium. The patients with delirium showed similar perioperative rSO_2 values as those without, in terms of the median lowest rSO_2 values (55% vs. 56%; P=0.876) and incidence (22%, both) and duration of decline of rSO2<80% of the baseline values. The serially assessed hemodynamic variables, hematocrit levels, and blood gas analysis variables were also similar between the groups, except for the number of hypotensive events per patient, which was higher in the patients with delirium than in those without (4, interquartile range [IQR] 3 to 6 vs. 2, IQR: 1to 3; P=0.014). The degree and duration of decrease of the perioperative rSO_2 measurements were not associated with delirium in elderly patients after spinal surgery (18).

[0059] Three-dimensional Arterial Spin Labeling (ASL) MRI was performed before surgery in a cohort of 146 prospectively enrolled subjects $\geq$ 70 years old scheduled to undergo elective surgery. The prospective association between ASL-derived measures of cerebral blood flow (CBF) before surgery with postoperative delirium incidence and severity using whole-brain and globally normalized voxel-wise analysis, was investigated. In addition, the cross-sectional association of CBF with patients' baseline performance on specific neuropsychological tests, and with a composite general cognitive performance measure (GCP), was investigated. Out of 146 subjects, 32 (22%) developed delirium. No significant association was found between global and voxel-wise CBF with delirium incidence or severity. The most significant positive associations was found between CBF of the posterior cingulate and precuneus and the Hopkins Verbal Learning Test - Revised total score, Visual Search and Attention Test (VSAT) score and the GCP composite. VSAT score was also strongly associated with right parietal lobe CBF. ASL can

be employed in a large, well-characterized older cohort to examine associations between CBF and age-related cognitive performance. Although ASL CBF measures in regions previously associated with preclinical Alzheimer's Disease were correlated with cognition, they were not found to be indicators of baseline pathology that may increase risk for delirium (19).

[0060] Oxidative stress may be involved in occurrence of postoperative delirium (POD) and cognitive dysfunction (POCD). 8-iso-Prostaglandin F2α (8-iso-PGF2α), an isoprostane derived from arachidonic acid via lipid peroxidation, is considered a gold standard for measuring oxidative stress. The ability of postoperative plasma 8-iso-PGF2α levels to predict POD and POCD in elderly patients undergoing hip fracture surgery was investigated. Postoperative plasma 8-iso-PGF2α levels of 182 patients were measured by an enzyme-linked immunosorbent assay. The relationships between plasma 8-iso-PGF2α levels and the risk of POD and POCD, was assessed using a multivariate analysis. Plasma 8-iso-PGF2α levels and age were identified as the independent predictors for POD and POCD. Based on areas under receiver operating characteristic curve, the predictive values of 8-iso-PGF2α were obviously higher than those of age for POD and POCD. In a combined logistic-regression model, 8-iso-PGF2α significantly enhanced the areas under curve of age for prediction of POD and POCD. Postoperative plasma 8-iso-PGF2α levels may have the potential to predict POD and POCD in elder patients undergoing hip fracture surgery (20).

[0061] Risk factors for delirium following cardiac surgery are incompletely understood. It was investigated whether intra-operative pathophysiological alterations and therapeutic interventions influence the risk of post-operative delirium. A retrospective cohort study was performed in a 12-bed cardiosurgical intensive care unit (ICU) of a university hospital and included patients consecutively admitted after cardiac surgery during a 2-month period. The diagnosis of delirium was made clinically using validated scores. Comparisons between patients with and without delirium were performed with non-parametric tests. Logistic regression was applied to identify independent risk factors. Results are given as number (percent) or median (range). Of the 194 consecutive post-cardiac surgery patients, 50 (26%) developed delirium during their ICU stay. Univariate analysis revealed that significant differences between patients with and without delirium occurred in the following intra-operative variables: duration of cardiopulmonary bypass (184 [72-299] *vs* 113 (37-717) minutes, $p < 0.001$), lowest mean arterial pressure (50 [30-70] *vs* 55 [30-75] mmHg, $p = 0.004$), lowest haemoglobin level (85 [56-133] *vs* 98 [53-150] g/L, $p = 0.005$), lowest body temperature (34.5 [24.4-37.2] *vs* 35.1 [23.9-37.2] °C, $p = 0.035$), highest noradrenaline support (0.11 [0.00-0.69] *vs* 0.07 [0.00-0.42] µg/kg/minute,

p = 0.001), and frequency of red blood cell transfusions (18 [36%] *vs* 26 [18%], p = 0.018) and platelet transfusions (23 [46%] *vs* 24 [17%], p < 0.001). Only platelet transfusions remained an independent risk factor in the multivariate analysis (p < 0.001). In patients undergoing cardiac surgery, various intra-operative events, such as transfusion of platelets, were risk factors for the development of a post-operative delirium in the ICU. Further research is needed to unravel the underlying mechanisms (21).

[0062] Bilge *et al*. (22) aimed to determine the risk factors and the incidence of delirium in patients who were followed postoperatively in our surgical intensive care unit for 24 h using the confusion assessment method (CAM). After obtaining approval from the ethics committee, 250 patients were included in the study. Patients who were operated under general anaesthesia or regional anaesthesia and followed in the surgical intensive care unit were evaluated by the Ramsay Sedation Scale on the first postoperative day. CAM was applied to the patients who had a Ramsey Sedation Score of ≤4. Patients' age, gender, American Society of Anesthesiologists (ASA) scores, preoperative risk factors, type of anaesthesia, operation time, intra-operative procedures, pain scores evaluated by the visual analogue scale (VAS) and postoperative analgesia methods were recorded. The incidence of delirium was found to be 18.4%. The average age of patients who developed delirium was greater than the others (68.8±12.7 and 57.6±12, p=0.001, respectively). It was observed that a one-unit increase in the ASA score resulted in a 3.3-fold increase in the risk of delirium. The incidence of delirium in patients undergoing regional anaesthesia was 34.6%, whereas it was 16.5% in patients receiving general anaesthesia (p=0.024). The existence of preoperative diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) was shown to improve the development of delirium (p<0.05). Delirium incidence was significantly higher in patients who were administered meperidine for postoperative analgesia (p=0.013). The VAS scores of patients who developed delirium were found to be significantly higher (p=0.006). As a result, it was found that older age, high ASA score, preoperative DM and COPD are important risk factors for the development of delirium. Regional anaesthesia, high postoperative pain scores and meperidine use were observed to be associated with the development of delirium. In the postoperative period, addition of CAM, a simple measurement technique, to the daily follow-up forms can provide the early recognition of delirium, which is often underdiagnosed. It was concluded that the identification and prevention of effective risk factors have the primary importance for postoperative delirium (22).

[0063] Delirium after cardiac surgery is a major problem. The exact mechanisms behind delirium are not understood. Potential pathways of delirium include neurotransmitter interference, global cognitive disorder, and neuroinflammation. Several predisposing and precipitating risk factors have been identified for postoperative delirium. The development of delirium following cardiac surgery is associated with worse outcomes in the perioperative period. Multiple interventions are being explored for the prevention and treatment of delirium. Studies investigating the potential roles of biomarkers in delirium as well as pharmacological interventions to reduce the incidence and duration of delirium are necessary to mitigate this negative outcome (23).

[0064] Perhaps the most frequently described mechanism of brain injury in CABG surgery is based on the recognition that microemboli are generated by the surgeon manipulating the heart and aorta, through cardiotomy suctioning, and by the cardiopulmonary bypass circuit itself. Microemboli can be detected intraoperatively as high-intensity transient signals by transcranial Doppler sonography. They have the potential to lodge in cerebral microvasculature, impairing blood supply to the brain and thus cerebral oxygenation. Several phases during cardiac surgery have been associated with increased risk of embolic showers. Aortic cannulation and clamping (during application of cardiopulmonary bypass) increase the high-intensity transient signal rate, particularly if there is extensive atheroma in the ascending aorta (24). It is not surprising, therefore, that most (81%) microemboli are generated at the point of aortic cross-clamp release (25). Retaining the shed mediastinal blood with cardiotomy suckers provides an additional source of lipid emboli and other fragments (26).

Lipid Neuroprotection

[0065] The harmony and function of the complex brain circuits and synapses are sustained mainly by excitatory and inhibitory neurotransmission, neurotrophins, gene regulation, and factors, many of which are incompletely understood. A common feature of brain circuit components, such as dendrites, synaptic membranes, and other membranes of the nervous system, is that they are richly endowed in docosahexaenoic acid (DHA), the main member of the omega-3 essential fatty acid family. DHA is avidly retained and concentrated in the nervous system and known to play a role in neuroprotection, memory, and vision. Only recently has it become apparent why the surprisingly rapid increases in free (unesterified) DHA pool size take place at the onset of seizures or brain injury. This phenomenon began to be clarified by the discovery of neuroprotectin D1 (NPD1), the first-uncovered bioactive docosanoid formed from

free DHA through 15-lipoxygenase-1 (15-LOX-1). NPD1 synthesis includes, as agonists, oxidative stress and neurotrophins. The evolving concept is that DHA-derived docosanoids set in motion endogenous signaling to sustain homeostatic synaptic and circuit integrity. NPD1 is anti-inflammatory, displays inflammatory resolving activities, and induces cell survival, which is in contrast to the pro-inflammatory actions of the many of omega-6 fatty acid family members. Bazan *et al*. (27) highlighted studies relevant to the ability of DHA to sustain neuronal function and protect synapses and circuits in the context of DHA signalolipidomics. DHA signalolipidomics comprises the integration of the cellular/tissue mechanism of DHA uptake, its distribution among cellular compartments, the organization and function of membrane domains containing DHA phospholipids, and the precise cellular and molecular events revealed by the uncovering of signaling pathways regulated by docosanoids endowed with prohomeostatic and cell survival bioactivity. Therefore, this approach offers emerging targets for prevention, pharmaceutical intervention, and clinical translation involving DHA-mediated signaling.

[0066] The significance of the selective enrichment in omega-3 essential fatty acids in photoreceptors and synaptic membranes of the nervous system has remained, until recently, incompletely understood. While studying mechanisms of cell survival in neural degeneration, Palacios-Pelaez *et al*. (28) discovered a docosanoid synthesized from unesterified docosahexaenoic acid (DHA) by a 15-lipoxygenase (15-LOX), which they called neuroprotectin D1 (NPD1; 10R,17S-dihydroxy-docosa-4Z,7Z, 11E,13E,15E,19Z hexaenoic acid). This lipid mediator is a docosanoid because it is derived from the 22 carbon (22C) precursor DHA, unlike eicosanoids, which are derived from the 20 carbon (20C) arachidonic acid (AA) family member of essential fatty acids. They discovered that NPD1 is promptly made in response to oxidative stress, as a response to brain ischemia-reperfusion, and in the presence of neurotrophins. NPD1 is neuroprotective in experimental brain damage, in oxidative-stressed retinal pigment epithelial (RPE) cells, and in human brain cells exposed to amyloid-beta (Aβ) peptides. They thus envision NPD1 as a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by imbalances in normal neural function. They provide here, in three sections, recent experimental examples that highlight the specificity and potency of NPD1 spanning beneficial bioactivity during initiation and early progression of neurodegeneration: 1) during retinal signal phototransduction; 2) during brain ischemia-reperfusion; and 3) in Alzheimer's disease (AD) and stressed human brain cell models of AD. From this experimental evidence, they conclude that DHA-derived NPD1 regulation targets upstream events of brain cell apoptosis, as well as neuro-

inflammatory signaling, promoting and maintaining cellular homeostasis, and restoring neural and retinal cell integrity.

[0067] Deficiency in docosahexaenoic acid (DHA) is associated with impaired visual and neurological development, cognitive decline, macular degeneration, and other neurodegenerative diseases. DHA is concentrated in phospholipids of the brain and retina, with photoreceptor cells having the highest DHA content of all cell membranes. The discovery that neuroprotectin D1 (NPD1; 10R, 17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) is a bioactive mediator of DHA sheds light on the biological importance of this fatty acid. In oxidative stress-challenged human retinal pigment epithelial (RPE) cells, human brain cells, or brain ischemia-reperfusion, NPD1 synthesis is enhanced as a response for sustaining homeostasis. Thus, neurotrophins, Aβ peptide ($A\beta_{42}$), calcium ionophore A23187, interleukin-1β (IL-1β), or DHA supply enhances NPD1 synthesis. NPD1, in turn, upregulates the antiapoptotic proteins of the Bcl-2 family and decreases the expression of proapoptotic Bcl-2 family members. In human neural cells, DHA attenuates $A\beta_{42}$ secretion, resulting in concomitant formation of NPD1. NPD1 repressed $A\beta_{42}$-triggered activation of proinflammatory genes and upregulated the antiapoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1(A1) in human brain cells in culture. Overall, NPD1 signaling regulates brain and retinal cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress $A\beta_{42}$-induced neurotoxicity and other forms of cell injury. These in turn support homeostasis during brain and retinal aging, counteract inflammatory signaling, and downregulate events that support the initiation and progression of neurodegenerative disease (29).

[0068] Maciá-Botejara *et al*. (30) studied the changes occurring in brain lipid composition after the administration of total parenteral nutrition (TPN) by comparing two lipid emulsions, one with long-chain triacylglycerols (LCT) and the other with long-chain and medium-chain triacylglycerols (MCT/LCT 50%/50%). They used 21 young New Zealand rabbits divided into three groups of seven animals each. Two groups were subjected to TPN for 7 d, with each group receiving using one of two different lipid emulsions: Intralipid 20% (group LCT) and Lipofundin MCT/LCT 20% (group MCT/LCT). The third control group received an oral diet and underwent the same surgical procedure with the administration of intravenous saline solution. The energy administered in the TPN formulas was non-protein 100 $kcal \cdot kg^{-1} \cdot d^{-1}$, with 40% corresponding to fats. There were modest increases in plasma cholesterol and triacylglycerols. In the brain tissue, there was a decrease of phosphatidylcholine in animals with TPN, which was greater in group LCT. There were no significant differences in the overall percentage distribution of brain fatty

acids among the groups. The lipid emulsions administered in TPN, especially those prepared exclusively with LCT, cause changes in the brain lipid polar fractions of young rabbits.

The Lipid Sink Effect

[0069] Papadopoulou *et al*. (31) hypothesized that by substituting a dye surrogate in place of local anesthetic, they could visually demonstrate dye sequestration by lipid emulsion that would be dependent on both dye lipophilicity and the amount of lipid emulsion used. They selected 2 lipophilic dyes, acid blue 25 and Victoria blue, with log P values comparable to lidocaine and bupivacaine, respectively. Each dye solution was mixed with combinations of lipid emulsion and water to emulate "lipid rescue" treatment at dye concentrations equivalent to fatal, cardiotoxic, and neurotoxic local anesthetic plasma concentrations. The lipid emulsion volumes added to each dye solution emulated equivalent intravenous doses of 100, 500, and 900 mL of 20% Intralipid in a 75-kg adult. After mixing, the samples were separated into a lipid-rich supernatant and a lipid-poor subnatant by heparin flocculation. The subnatants were isolated, and their colors compared against a graduated dye concentration scale.

[0070] Lipid emulsion addition resulted in significant dye acquisition by the lipid compartment accompanied by a reduction in the color intensity of the aqueous phase that could be readily observed. The greatest amount of sequestration occurred with the dye possessing the higher log P value and the greatest amount of lipid emulsion. This study provides a visual demonstration of the lipid sink effect. It supports the theory that lipid emulsion may reduce the amount of free drug present in plasma from concentrations associated with an invariably fatal outcome to those that are potentially survivable.

[0071] Local anesthetic (LA) intoxication with cardiovascular arrest is a potential fatal complication of regional anesthesia. Lipid resuscitation has been recommended for the treatment of LA-induced cardiac arrest. Mauch *et al*. (32) compared four different rescue regimens using epinephrine and/or lipid emulsion and vasopressin to treat cardiac arrest caused by bupivacaine intoxication. Twenty-eight piglets were randomized into four groups (4 × 7), anesthetized with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via central venous catheter at a rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ until circulatory arrest. Bupivacaine infusion and sevoflurane were then stopped, chest compression was started, and the pigs were ventilated with 100% oxygen. After 1 min, epinephrine 10 $\mu g \cdot kg^{-1}$ (group 1), Intralipid(→) 20% 4 $ml \cdot kg^{-1}$ (group 2), epinephrine 10 $\mu g \cdot kg^{-1}$ + Intralipid(→) 4 $ml \cdot kg^{-1}$ (group 3) or 2 IU vasopressin + Intralipid(→) 4 $ml \cdot kg^{-1}$ (group 4) were administered. Secondary epinephrine doses were given

after 5 min if required. Survival was 71%, 29%, 86%, and 57% in groups 1, 2, 3, and 4. Return of spontaneous circulation was regained only by initial administration of epinephrine alone or in combination with Intralipid(→). Piglets receiving the combination therapy survived without further epinephrine support. In contrast, in groups 2 and 4, return of spontaneous circulation was only achieved after secondary epinephrine rescue.

[0072] In cardiac arrest caused by bupivacaine intoxication, first-line rescue with epinephrine and epinephrine + Intralipid(→) was more effective with regard to survival than Intralipid(→) alone and vasopressin + Intralipid(→) in this pig model (33).

[0073] Local anesthetic (LA) intoxication with severe hemodynamic compromise is a potential catastrophic event. Lipid resuscitation has been recommended for the treatment of LA-induced cardiac arrest. However, there are no data about effectiveness of Intralipid for the treatment of severe cardiovascular compromise prior to cardiac arrest. Aim of this study was to compare effectiveness of epinephrine and Intralipid for the treatment of severe Hemodynamic compromise owing to bupivacaine intoxication, anesthetized Piglets were with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via a central venous catheter at a rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ until invasively measured mean arterial pressure (MAP) dropped to 50% of the initial value. Bupivacaine infusion was then stopped, and epinephrine 3 $\mu g \cdot kg^{-1}$ (group 1), Intralipid(→) 20% 2 $ml \cdot kg^{-1}$ (group 2), or Intralipid 20% 4 $ml \cdot kg^{-1}$ (group 3) was immediately administered. Twenty-one piglets (3 × 7), were recorded. All animals in group 1 (100%) but only four of seven (57%) piglets in group 2 and group 3, respectively, survived. Normalization of hemodynamic parameters (HR, MAP) and ET(CO_2) was fastest in group 1 with all piglets achieving HR and MAP values. hemodynamic compromise owing to bupivacaine intoxication in piglets, first-line rescue with epinephrine was more effective than Intralipid with regard to survival as well as normalization of hemodynamic parameters and ET(CO_2) (34).

[0074] Intravenous lipid emulsion (ILE) has been proposed as a rescue therapy for severe local anesthetic drugs toxicity, but experience is limited with other lipophilic drugs. An 18-year-old healthy woman was admitted 8 h after the voluntary ingestion of sustained-release diltiazem (3600 mg), with severe hypotension refractory to fluid therapy, calcium salts, and high-dose norepinephrine (6.66 μg/kg/min). Hyperinsulinemic euglycemia therapy was initiated and shortly after was followed by a protocol of ILE (intralipid 20%, 1.5 ml/kg as bolus, followed by 0.25 ml/kg over 1h). The main finding attributed to ILE was an apparent rapid decrease in insulin resistance, despite a prolonged serum diltiazem elimination half-life. Diltiazem is a lipophilic cardiotoxic drug, which could be sequestered in an expanded plasma lipid phase. The mechanism

of action of ILE is not known, including its role in insulin resistance and myocardial metabolism in calcium-channel blocker poisoning (35).

Conclusions

[0075] A new treatment for POD by intravenous Intralipid injection in the recovery room is first suggested in the medical literature.

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CLAIMS

1. Intralipid for use in treatment of Alzheimer's disease.

2. The intralipid according to claim 1, wherein said treatment of Alzheimer's disease is preventative treatment, e.g. for patients' in risk of developing Alzheimer's disease.

3. The intralipid according to claim 1, wherein said treatment of Alzheimer's disease is ameliorating the symptoms of Alzheimer's disease, stopping the progression of the disease, and/or eliminating the disease and/or improving the patients' condition, e.g. by promotion of neuronal tissue restoration and/or neuronal functional recovery.

4. The intralipid according to claim 1, wherein said intralipid is formulated for injection into the cerebrospinal fluid (CSF) or the blood stream of a patient.

5. A composition comprising intralipid for treatment of Alzheimer's disease.

6. The composition according to claim 5, further comprises a pharmaceutically acceptable carrier adapted for injection.

7. The composition according to claim 5 or 6, which is designed for administration into the cerebrospinal fluid (CSF) or the blood stream.

8. A method for treating Alzheimer's disease comprising administering to an individual in need an effective amount of intralipid or a composition comprising same.

9. The method according to claim 8, comprising injecting said intralipid or said composition comprising same into the CSF or the blood stream of said individual.

10. Intralipid for use in treatment of postoperative delirium (POD).

11. The intralipid according to claim 10, wherein said treatment of POD is preventative treatment, e.g. for patients' in risk of developing POD.

12. The intralipid according to claim 10, wherein said treatment of POD is eliminating the disease and/or improving the patients' condition, e.g. by promotion of neuronal tissue restoration and/or neuronal functional recovery.

13. The intralipid according to claim 10, wherein said intralipid is formulated for injection into the cerebrospinal fluid (CSF) or the blood stream of a patient.

14. A composition comprising intralipid for treatment of postoperative delirium (POD).

15. The composition according to claim 14, further comprises a pharmaceutically acceptable carrier adapted for injection.

16. The composition according to claim 14 or 15, which is designed for administration into the cerebrospinal fluid (CSF) or the blood stream.

17. A method for treating postoperative delirium (POD) comprising administering to an individual in need an effective amount of intralipid or a composition comprising same.

18. The method according to claim 17, comprising injecting said intralipid or said composition comprising same into the CSF or the blood stream of said individual.

19. The intralipid according to any one of claims 1-4 and 10-13, which is any lipid emulsion.

20. The composition according to any one of claims 5-7 and 14-16, wherein said intralipid is any lipid emulsion.

21. The method according to any one of claims 8, 9, 17 and 18, wherein said intralipid is any lipid emulsion.