Intralipid and the Immune system

Joseph Eldor, MD

J Antimicrob Chemother. 2012 Jul;67(7):1716-21. Epub 2012 Apr 11.

Pharmacokinetics, tissue distribution and immunomodulatory effect of intralipid formulation of nystatin in mice.

Semis R, Nili SS, Munitz A, Zaslavsky Z, Polacheck I, Segal E.

Source

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Abstract

OBJECTIVES:

We developed a novel lipid formulation of nystatin suitable for parenteral administration, nystatin-intralipid (NYT-IL), with antifungal activity and reduced toxicity in mice. We investigated the pharmacokinetics, tissue distribution and immunomodulatory effect of NYT-IL in mice.

METHODS:

Nystatin levels in serum and organs were determined using HPLC after NYT-IL or nystatin administration in mice. The levels of the pro-inflammatory cytokines tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) and the anti-inflammatory cytokine interleukin 10 (IL-10) produced by splenocytes from mice injected with NYT-IL or nystatin were evaluated by an ELISA assay.

RESULTS:

Injection of NYT-IL resulted in similar levels and similar kinetics of nystatin in serum, higher concentrations in the liver and lower concentrations in the kidneys, in comparison with nystatin injection. Injection of mice with NYT-IL yielded higher levels of IL-10 than that of nystatin, whereas the levels of TNF-α and IFN-γ induced by NYT-IL were lower than those elicited by nystatin.

CONCLUSIONS:

Since polyene treatment is associated with nephrotoxicity, lower levels of nystatin in the kidneys following NYT-IL injection suggest the possibility of reduced toxicity. As the acute infusion-related adverse effects associated with polyene treatment are considered to be induced by pro-inflammatory cytokines, a higher level of anti-inflammatory and lower levels of pro-inflammatory cytokines elicited by NYT-IL administration suggest the possibility of amelioration of such effects. In summary, the altered pharmacokinetics, tissue distribution and immune response due to the use of this intralipid formulation of nystatin merit further research towards the development of a therapeutic agent against invasive mycoses.

Crit Care Med. 2012 Jun;40(6):1792-8.

A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid

emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition.

Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP, Peng L, Morris T, Luo M, Garcia H, Thomas C, Newton CA, Ziegler TR.

Source

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Abstract

OBJECTIVE:
Parenteral nutrition has been associated with metabolic and infectious complications in intensive care unit patients. The underlying mechanism for the high risk of complications is not known but may relate to the proinflammatory effects of soybean oil-based lipid emulsions, the only Food and Drug Administration-approved lipid formulation for clinical use.

DESIGN:
Prospective, double-blind, randomized, controlled trial.

SETTING:
Medical-surgical intensive care units from a major urban teaching hospital and a tertiary referral university hospital.

PATIENTS:
Adult medical-surgical intensive care unit patients.

INTERVENTION:
Parenteral nutrition containing soybean oil-based (Intralipid) or olive oil-based (ClinOleic) lipid emulsions.

MEASUREMENTS:
Differences in hospital clinical outcomes (nosocomial infections and noninfectious complications), hospital length of stay, glycemic control, inflammatory and oxidative stress markers, and granulocyte and monocyte functions between study groups.

RESULTS:
A total of 100 patients were randomized to either soybean oil-based parenteral nutrition or olive oil-based parenteral nutrition for up to 28 days. A total of 49 patients received soybean oil-based parenteral nutrition (age 51 ± 15 yrs, body mass index 27 ± 6 kg/m2, and Acute Physiology and Chronic Health Evaluation II score 15.5 ± 7 [±SD]), and a total of 51 patients received olive oil-based lipid emulsion in parenteral nutrition (age 46 ± 19 yrs, body mass index 27 ± 8 kg/m2, and Acute Physiology and Chronic Health Evaluation II score 15.1 ± 6 [±SD]) for a mean duration of 12.9 ± 8 days. The mean hospital blood glucose concentration during parenteral nutrition was 129 ± 14 mg/dL, without differences between groups. Patients treated with soybean oil-based and olive oil-based parenteral nutrition had a similar length of stay (47 ± 47 days and 41 ± 36 days, p = .49), mortality (16.3% and 9.8%, p = .38), nosocomial infections (43% vs. 57%, p = .16), and acute renal failure (26% vs. 18%, p = .34). In addition, there were no differences in inflammatory and oxidative stress markers or in granulocyte and monocyte functions between groups.

CONCLUSION:
The administration of parenteral nutrition containing soybean oil-based and olive oil-based lipid emulsion resulted in similar rates of infectious and noninfectious complications and no differences in glycemic control, inflammatory and oxidative stress markers, and immunefunction in critically ill adults.

Am J Physiol Gastrointest Liver Physiol. 2012 Jun 1;302(11):G1292-300. Epub 2012 Mar 29.

Activation of rat intestinal mucosal mast cells by fat absorption.

Ji Y, Sakata Y, Yang Q, Li X, Xu M, Yoder S, Langhans W, Tso P.

Source

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Abstract

Previous studies have linked certain types of gut mucosal immune cells with fat intake. We determined whether fat absorption activates intestinal mucosal mast cells (MMC), a key component of the gut mucosal immune system. Conscious intestinal lymph fistula rats were used. The mesenteric lymph ducts were cannulated, and the intraduodenal (i.d.) tubes were installed for the infusion of Liposyn II 20% (an intralipid emulsion). Lymphatic concentrations of histamine, rat MMC protease II (RMCPII), a specific marker of rat intestinal MMC degranulation, and prostaglandin D(2) (PGD(2)) were measured by ELISA. Intestinal MMC degranulation was visualized by immunofluorescent microscopy of jejunum sections taken at 1 h after Liposyn II gavage. Intraduodenal bolus infusion of Liposyn II 20% (4.4 kcal/3 ml) induced approximately a onefold increase in lymphatic histamine and PGD(2), □20-fold increase in lymphatic RMCPII, but only onefold increase in peripheral serum RMCPII concentrations. Release of RMCPII into lymph increased dose dependently with the amount of lipid fed. In addition, i.d. infusion of long-chain triacylglycerol trilinolein (C18:2 n-6, the major composite in Liposyn II) significantly increased the lymphatic RMCPII concentration, whereas medium-chain triacylglycerol tricaprylin (C8:0) did not alter lymph RMCPII secretion. Immunohistochemistry image revealed the degranulation of MMC into lamina propria after lipid feeding. These novel findings indicate that intestinal MMC are activated and degranulate to release MMC mediators to the circulation during fat absorption. This action of fatty acid is dose and chain length dependent.

J Reprod Immunol. 2012 Jan;93(1):38-40. Epub 2011 Dec 21.

Intralipid therapy for recurrent implantation failure: new hope or false dawn?

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Source

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Abstract

Recurrent embryo implantation failure (RIF) is a disorder with potentially devastating physiological and psychological manifestations for those affected. Although its prevalence is not uncommon, many of the mechanisms involved still require elucidation. Both organ-specific and systemic autoimmunity are associated with an increased prevalence of recurrent miscarriage and reproductive failure, rendering the role of the maternal immunological system in fertility a key concept. It is believed by some that central to this theme is the maternal cytokine profile, with particularly T-helper (Th) cells. Immune modulating therapies have therefore been mooted as potential therapeutic strategies. Recent reports of high pregnancy rates achievable in women with RIF have added fuel to the debate regarding the

effectiveness of intralipid in modulating the immunesystem. We would like to assess if there is sufficient current evidence of acceptable quality to permit an assumption that intralipid therapy is an effective treatment for women undergoing repeated assisted reproduction cycles. We have concluded that appropriately controlled, large-scale, confirmatory studies are necessary to prove the efficacy of intralipid before it can be recommended for routine use.

J Clin Endocrinol Metab. 2011 Oct;96(10):3207-16. Epub 2011 Aug 10.

Substitution of standard soybean oil with olive oil-based lipid emulsion in parenteral nutrition: comparison of vascular, metabolic, and inflammatory effects.

Siqueira J, Smiley D, Newton C, Le NA, Gosmanov AR, Spiegelman R, Peng L, Osteen SJ, Jones DP,Quyyumi AA, Ziegler TR, Umpierrez GE.

Source

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Abstract

CONTEXT:
Soybean oil-based lipid emulsions are the only Food and Drug Administration-approved lipid formulation for clinical use in parenteral nutrition (PN). Recently concerns with its use have been raised due to the proinflammatory effects that may lead to increased complications because they are rich in ω-6 polyunsaturated fatty acids.

METHODS:
This was a prospective, randomized, controlled, crossover study comparing the vascular, metabolic, immune, and inflammatory effects of 24-h infusion of PN containing soybean oil-based lipid emulsion (Intralipid), olive oil-based (ClinOleic), lipid free, and normal saline in 12 healthy subjects.

RESULTS:
Soybean oil-PN increased systolic blood pressure compared with olive oil-PN ($P < 0.05$). Soybean oil PN reduced brachial artery flow-mediated dilatation from baseline (-23% at 4 h and -25% at 24 h, both $P < 0.01$); in contrast, olive oil PN, lipid free PN, and saline did not change either systolic blood pressure or flow-mediated dilatation. Compared with saline, soybean oil PN, olive oil PN, and lipid free PN similarly increased glucose and insulin concentrations during infusion ($P < 0.05$). There were no significant changes in plasma free fatty acids, lipid profile, inflammatory and oxidative stress markers, immune function parameters, or sympathetic activity between soybean oil- and olive oil-based lipid emulsions.

CONCLUSION:
The 24-h infusion of PN containing soybean oil-based lipid emulsion increased blood pressure and impaired endothelial function compared with PN containing olive oil-based lipid emulsion and lipid-free PN in healthy subjects. These vascular changes may have significant implications in worsening outcome in subjects receiving nutrition support. Randomized controlled trials with relevant clinical outcome measures are needed in patients receiving PN with olive oil-based and soybean oil-based lipid emulsions.

J Orthop Trauma. 2011 Aug;25(8):511-5.

Androstenediol exerts salutary effects on chemokine response after trauma-hemorrhage and sepsis in mice.

Brunnemer U, Zeckey C, Hildebrand F, Frink M, Mommsen P, van Griensven M, Andruszkow H, Krettek C,Barkhausen T.

Source

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Abstract

OBJECTIVES:

The pathogenesis of multiple organ dysfunction syndrome and sepsis after polytrauma is related to the posttraumatic immune response and the associated release of inflammatory mediators. There exists a gender dimorphism in the posttraumatic host response. Sex steroids are believed to beneficially modulate the posttraumatic immune response. The specific effect of androstenediol on chemokines after trauma is unknown. We investigated whether the application of androstenediol has an effect on plasma chemokine levels and the associated remote organ damage in a two-hit mouse-model of trauma-hemorrhage, cecal ligation, and cecal puncture.

MATERIALS AND METHODS:

Traumatic hemorrhage was induced followed by androstenediol application and volume resuscitation. Thereafter, androstenediol was given once daily in combination with a vehicle (Intralipid). The control group was injected with a solution containing only the vehicle at the same time points as the treatment groups' androstenediol applications. Sepsis was induced by cecal ligation and cecal puncture 48 hours afterward. Four hours after cecal ligation and cecal puncture, plasma measurements of chemokines were performed. Pulmonary infiltration by polymorphonuclear lymphocytes was measured by immunhistochemical staining and myeloperoxidase measurements were taken.

RESULTS:

Application of androstenediol led to significantly decreased monocyte chemoattractant protein-1, monocyte chemoattractant protein-3, macrophage inflammatory protein-1α, and macrophage inflammatory protein-1β levels compared with the control animals after trauma-hemorrhage, cecal ligation, and cecal puncture ($P < 0.05$). Pulmonary infiltration and myeloperoxidase activity were significantly decreased in androstenediol-treated animals ($P < 0.05$).

CONCLUSION:

Androstenediol modulates the immune response after trauma-hemorrhage, cecal ligation, and cecal puncture by reducing systemic chemokine levels, which are known to directimmune cells into the tissue possibly leading to organ damage. Androstenediol represents a potential therapeutic agent after major trauma in high-risk patients.

Clin Exp Obstet Gynecol. 2010;37(2):81-3.

A practical approach to the prevention of miscarriage: Part 3--Passive immunotherapy.

Check JH.

Abstract

PURPOSE:

To evaluate the efficacy of passive immunotherapy in preventing miscarriage.

METHODS:
Studies both pro and con concerning intravenous immunoglobulin therapy (IVIG) in preventing miscarriage were evaluated. A new therapy of i.v. intralipid infusion is also reviewed.
RESULTS:
Intravenous immunoglobulin therapy may be effective but it is necessary to use it prior to conception and monthly thereafter. Some brands are more potent than others. The data concerning intralipid i.v. infusion involves only small case series but the results from one study were encouraging though we could not personally substantiate these findings.
CONCLUSIONS:
Intravenous immunoglobulin therapy is very expensive. In the author's opinion there are no immunological studies that can determine if a woman needs immune suppression. The best way to decide is the history--the more miscarriages without any other identifiable cause the more likely passive immunotherapy may be helpful. If intralipid proves as efficacious as IVIG it will be a lot less expensive.

Ann Pharmacother. 2010 Apr;44(4):688-700.

State of the art review: Intravenous fat emulsions: Current applications, safety profile, and clinical implications.

Mirtallo JM, Dasta JF, Kleinschmidt KC, Varon J.

Source

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Abstract
OBJECTIVE:
To review the current state of the science regarding intravenous fat emulsions (IVFEs), with an emphasis on their safety profile.

DATA SOURCES:
Articles were identified via a search of the MEDLINE database, including publications from 1979 to December 2009, using a search string that included the terms parenteral nutrition, lipid emulsion, fat emulsion, IVFE, safety, adverse effect, neonate intralipid, and terms describing a range of specific adverse events (AEs) such as pancreatitis.
STUDY SELECTION AND DATA EXTRACTION:
We selected articles that allowed us to compare the results of clinical trials involving delivery of medications via IVFEs with the historical use and effects of IVFEs in parenteral nutrition, with an emphasis on AEs. We focused on 2 drugs in current use that are administered intravenously in lipid emulsions: propofol and clevidipine.

DATA SYNTHESIS:
Clearance of the fat particles in IVFEs is mediated by the enzyme lipoprotein lipase. AEs are more likely if the rate or duration of IVFE administration exceeds the enzyme's clearance capacity. AEs are also more likely after administration of a 10% IVFE formulation than a 20% formulation, because the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity. AEs can be reduced by administering IVFEs at a dosage < or = 2.5 g/kg/day and at a rate < or = 0.11 g/kg/h. The anesthetic agent propofol, which is formulated in a 10% IVFE, has been used clinically for 25 years. Typical AEs associated with propofol use include infection, high plasma triglyceride concentrations, and

pancreatitis. Recent clinical trials involving clevidipine, which is formulated in a 20% IVFE, have demonstrated a low rate of lipid-related AEs.

CONCLUSIONS:
The results of this review demonstrate that IVFEs are well tolerated when administered in accordance with guideline recommendations.

Phys Med Biol. 2009 Nov 7;54(21):6739-55. Epub 2009 Oct 20.

Dynamic contrast-enhanced diffuse optical tomography (DCE-DOT): experimental validation with a dynamic phantom.

Unlu MB, Lin Y, Gulsen G.

Source

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Abstract

Dynamic contrast-enhanced diffuse optical tomography (DCE-DOT) can provide spatially resolved enhancement kinetics of an optical contrast agent. We undertook a systematic phantom study to evaluate the effects of the geometrical parameters such as the depth and size of the inclusion as well as the optical parameters of the background on the recovered enhancement kinetics of the most commonly used optical contrast agent, indocyanine green (ICG). For this purpose a computer-controlled dynamic phantom was constructed. An ICG-intralipid-water mixture was circulated through the inclusions while the DCE-DOT measurements were acquired with a temporal resolution of 16 s. The same dynamic study was repeated using inclusions of different sizes located at different depths. In addition to this, the effect of non-scattering regions was investigated by placing a second inclusion filled with water in the background. The phantom studies confirmed that although the peak enhancement varied substantially for each case, the recovered injection and dilution rates obtained from the percentage enhancement maps agreed within 15% independent of not only the depth and the size of the inclusion but also the presence of a non-scattering region in the background. Although no internal structural information was used in these phantom studies, it may be necessary to use it for small objects buried deep in tissue. However, the different contrast mechanisms of optical and other imaging modalities as well as imperfect co-registration between both modalities may lead to potential errors in the structural a priori. Therefore, the effect of erroneous selection of structural priors was investigated as the final step. Again, the injection and dilution rates obtained from the percentage enhancement maps were also immune to the systematic errors introduced by erroneous selection of the structural priors, e.g. choosing the diameter of the inclusion 20% smaller increased the peak enhancement 60% but changed the injection and dilution rates only less than 10%.

Nutr Metab (Lond). 2008 Jul 14;5:19.

Unsaturated long-chain fatty acids induce the respiratory burst of human neutrophils and monocytes in whole blood.

Jüttner B, Kröplin J, Coldewey SM, Witt L, Osthaus WA, Weilbach C, Scheinichen D.

Source

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Abstract

BACKGROUND:
It is increasingly recognized that infectious complications in patients treated with total parenteral nutrition (TPN) may be caused by altered immune responses. Neutrophils and monocytes are the first line of defence against bacterial and fungal infection through superoxide anion production during the respiratory burst. To characterize the impact of three different types of lipid solutions that are applied as part of TPN formulations, we investigated the unstimulated respiratory burst activation of neutrophils and monocytes in whole blood.
METHODS:
Whole blood samples were incubated with LCT (Intralipid(R)), LCT/MCT (Lipofundin(R)) and LCT-MUFA (ClinOleic(R)) in three concentrations (0.06, 0.3 and 0.6 mg ml-1) for time periods up to one hour. Hydrogen peroxide production during the respiratory burst of neutrophils and monocytes was measured by flow cytometry.
RESULTS:
LCT and LCT-MUFA induced a hydrogen peroxide production in neutrophils and monocytes without presence of a physiological stimulus in contrast to LCT/MCT.

CONCLUSION:
We concluded that parenteral nutrition containing unsaturated oleic (C18:1) and linoleic (C18:2) acid can induce respiratory burst of neutrophils and monocytes, resulting in an elevated risk of tissue damage by the uncontrolled production of reactive oxygen species. Contradictory observations reported in previous studies may in part be the result of different methods used to determine hydrogen peroxide production.

World J Gastroenterol. 2008 Apr 21;14(15):2434-9.

Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients.

Liang B, Wang S, Ye YJ, Yang XD, Wang YL, Qu J, Xie QW, Yin MJ.

Source

Division of Surgical Oncology, Peking University People's Hospital, Beijing 100044, China.

Abstract

AIM:
To investigate the effect of omega-3 fatty acid parenteral supplementation postoperatively on clinical outcomes and immunomodulation in colorectal cancer patients.

METHODS:
Forty-two patients undergoing radical colorectal cancer resection with an indication for total parenteral nutrition postoperatively were enrolled in this prospective, double-blind, randomized, controlled study. Patients received total parenteral nutrition supplemented with either soybean oil (LCT; Intralipid, Fresenius-Kabi, SO group, n = 21) or a combination of omega-3 fish oil and soybean oil (LCT:fish oil = 5:1, fish oil; Omegaven, Fresenius-Kabi, FO group, n = 21), up to a total of 1.2 g lipid/kg per day for 7 d postoperatively. A same volume calorie and nitrogen was administrated. Routine blood test, biochemistry, systemic levels of

IL-6 and TNF-alpha, percentage of CD3+, CD4+, and CD8+ lymphocytes were evaluated preoperatively and on postoperative d 1 and 8. Patient outcome was evaluated considering mortality during the hospital stay, length of postoperative hospital stay, and occurrence of infectious complications.

RESULTS:

Both lipid regimens were well tolerated. No differences between the two groups were noticed in demographics, baseline blood test, biochemistry, serum levels of IL-6 and TNF-alpha, percentage of CD4+, CD8+ lymphocytes, and ratios of CD4+/CD8+. Compared with those on postoperative d 1, serum IL-6 levels on postoperative d 8 were significantly depressed in the FO group than in the reference group (-44.43 +/- 30.53 vs -8.39 +/- 69.08, P = 0.039). Simultaneously, the ratios of CD4+/CD8+ were significantly increased in the FO group (0.92 +/- 0.62 vs 0.25 +/- 1.22, P = 0.035). In addition, depression of serum TNF-alpha levels (-0.82 +/- 2.71 vs 0.27 +/- 1.67, P = 0.125) and elevation of CD3+ and CD4+ lymphocyte percentage (12.85 +/- 11.61 vs 3.84 +/- 19.62, P = 0.081, 17.80 +/- 10.86 vs 9.66 +/- 17.55, P = 0.084, respectively) were higher in the FO group than in the reference group. Patients in the FO group tended to need a shorter postoperative hospital stay (17.45 +/- 4.80 d vs 19.62 +/- 5.59 d, P = 0.19). No statistically significant difference was found when stratified to mortality and occurrence of infectious complications.

CONCLUSION:

Postoperative supplementation of omega-3 fatty acids may have a favorable effect on the outcomes in colorectal cancer patients undergoing radical resection by lowering the magnitude of inflammatory responses and modulating the immune response.

Transpl Immunol. 2008 Feb;18(4):349-51. Epub 2007 Oct 25.

Dyslipidemia can reduce the immunosuppressive effects of cyclosporine.

Pozzetto U, Citterio F, Fioravanti G, Navarra P, Boccalini F, Castagneto M.

Source

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Abstract

AIMS:

Dyslipidemia is a significant risk factor for the development of atherosclerotic disease and of chronic allograft rejection. Few data are available on the effects of dyslipidemia on the immunosuppressive action of immunosuppressive agents. We investigate the in vitro effects of lipids solution on the immunosuppressive action of cyclosporine (CsA).

METHODS:

Peripheral blood mononuclear cells (PBMC) were PHA or OKT3 activated in vitro with/without different concentrations of Intralipid solution (INT, range 0.5% to 15%). CsA inhibition of activation was measured after a 3 day incubation, by adding H3-thimidine. The intracellular concentration of CsA was measured by radioimmunoassay and related to the CsA inhibitory effects.

RESULTS:

Increasing INT concentration in the medium, CsA inhibition of PBMC activation by PHA or OKT3 was reduced from 72+/-13% to 8+/-2% and from 80+/-10% to 18+/-3%, respectively. A significant reduction of the intracellular CsA concentration was also evident with increasing INT concentrations and was related to the inhibitory activity of CsA.

CONCLUSIONS:

These results suggest that dyslipidemia may reduce the availability of intracellular CsA concentration to inhibit the immune activation process and may explain the relationship between dyslipidemia and chronic allograft loss.

Am J Physiol Endocrinol Metab. 2008 Feb;294(2):E371-9. Epub 2007 Dec 4.

Effect of short-term intralipid infusion on the immune response during low-dose endotoxemia in humans.

Krogh-Madsen R, Plomgaard P, Akerstrom T, Møller K, Schmitz O, Pedersen BK.

Source

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Abstract

Novel anti-inflammatory effects of insulin have recently been described, and insulin therapy to maintain euglycemia suppresses the plasma levels of free fatty acids (FFA) and increases the survival of critically ill patients. We aimed to explore the effect of short-term high levels of plasma FFA on the inflammatory response to a low dose of endotoxin. Fourteen healthy male volunteers underwent the following two trials in a randomized crossover design: 1) continuous infusion of 20%Intralipid [0.7 ml.kg(-1).h(-1) (1.54 g/kg)] for 11 h, and 2) infusion of isotonic saline for 11 h (control). In each trial, heparin was given to activate lipoprotein lipase, and an intravenous bolus of endotoxin (0.1 ng/kg) was given after 6 h of Intralipid/saline infusion. Blood samples and muscle and fat biopsies were obtained before the Intralipid/saline infusion and before as well as after infusion of an endotoxin bolus. Plasma levels of FFA, triglycerides, and glycerol were markedly increased during the Intralipid infusion. Endotoxin exposure induced an increase in plasma levels of TNF-alpha, IL-6, and neutrophils and further stimulated gene expression of TNF-alpha and IL-6 in both skeletal muscle and adipose tissue. The systemic inflammatory response to endotoxin was significantly pronounced during Intralipid infusion. Short-term hyperlipidemia enhances the inflammatory response to endotoxin, and skeletal muscle and adipose tissue are capable of producing essential inflammatory mediators after endotoxin stimulation.

Ups J Med Sci. 2007;112(1):21-37.

Performance characteristics of a cystatin C immunoassay with avian antibodies.

Sunde K, Nilsen T, Flodin M.

Source

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Abstract

BACKGROUND:

A new particle-enhanced turbidimetric immunoassay (PETIA) with avian antibodies for measuring serum/plasma cystatin C has been developed. The performance characteristics of the assay are described.

METHODS:

Measurements were performed on a Roche Modular P and on an Abbott Architect ci8200 using Gentian cystatin C immunoassay.

RESULTS:
Measuring range was 0.3-8.0 mg/L. Reference range was 0.57-1.09 mg/L. Total analysis time was 10 minutes. Linearity was absolute over the whole assay range. Recovery of samples and controls was within 98.6-109.4%. Total imprecision CV, measured over 20 days with two lots, was < or = 4.2%. Comparison with a particle enhanced nephelometric cystatin C immunoassay (PENIA) by linear regression resulted in a slope within 0.97-1.02 and intercept within +/-0.05 mg/L. Interference studies with drugs, anticoagulants, intralipid (< or = 11 g/L), triglycerides (< or = 14 g/L) and bilirubin (< or = 420 mg/L) showed no significant interference. Due to the use of avian antibodies, no interference with rheumatoid factor was observed. No carry-over was detected. Lower detection limit and lower quantification limit (CV < or = 6%) were both below 0.33 mg/L, which is less than the lowest standard. Sample stability was up to one month at 2-8 degrees C. Stability of the reagents at 2-8 degrees C was estimated to be 24 months. Stability of the reagents in use was minimum 9 weeks.
CONCLUSIONS:
Gentian cystatin C PETIA is shown to have excellent performance between methods . Interference results are improved due to avian antibodies and a broader span of the calibration curve. Avian antibodies are also known to have better immune response than mammalian antibodies towards mammalian antigens.

Free Radic Res. 2007 Jan;41(1):25-37.

Biologically active oxidized lipids (phytoprostanes) in the plant diet and parenteral lipid nutrition.

Karg K, Dirsch VM, Vollmar AM, Cracowski JL, Laporte F, Mueller MJ.

Source

Julius-von-Sachs-Institute for Biosciences, Pharmaceutical Biology, University of Wuerzburg, Julius-von-Sachs-Platz 2, D-97082, Wuerzburg, Germany.

Abstract
Phytoprostanes (PP) are autoxidation products of alpha-linolenate that are present in all plant tissues. Several classes of PP with a prostaglandin (PG) F1-, E1-, A1- and B1-like structure were identified and quantified by gas chromatography-mass spectrometry in vegetable oils and parenteral nutrition (intralipid). High levels of PP (0.09 up to 99 mg/l) were found even in apparently fresh vegetable oils. After oral consumption of olive or soybean oil, PPF1 were absorbed, found to circulate in plasma in conjugated form and excreted in free form into urine. Evidence is emerging that certain PP, such as the PPE1, may modulate the function of immune cells in a PG-like fashion. Here, we show that PPA1- and deoxy-PPJ1 display potent anti-inflammatory and apoptosis inducing activities similar to PGA1 and deoxy-PGJ2. Results of this study indicate that PP are novel, biologically active lipids in plant nutrition.

J Immunol. 2004 Jan 1;172(1):54-60.

Sensing environmental lipids by dendritic cell modulates its function.

Coutant F, Agaugué S, Perrin-Cocon L, André P, Lotteau V.

Source

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Abstract

Because of its oxidative modification during the acute-phase response to an aggression, low density lipoprotein (LDL) can be regarded as a source of lipid mediators that can act both to promote and inhibit inflammation. This can be exemplified by the production of anti-inflammatory oxidized fatty acids and proinflammatory lysophosphatidylcholine (LPC) during LDL oxidation. We have shown previously that oxidized LDL (oxLDL) plays an active role at the interface between innate and adaptive immunity by delivering instructive molecules such as LPC, which promotes mature dendritic cell (DC) generation from differentiating monocytes. It is shown in this study that LPC affects the signaling pathway of peroxisome proliferator-activated receptors (PPARs). LPC-induced DC maturation is associated with complete inhibition of PPARgamma activity and up-regulation of the activity of an uncharacterized nuclear receptor that bind peroxisome proliferator response element. Oxidized fatty acids generated during LDL oxidation are natural ligands for PPARgamma and inhibit oxLDL- and LPC-induced maturation. Inhibition experiments with synthetic PPARgamma ligands suggested a PPARgamma-dependent and independent effect of LPC on DC maturation. Therefore, the relative amount of oxidized fatty acids and LPC influences the immunological functions of oxLDL on DC, in part by regulating the PPAR pathway. By sensing the biochemical composition of lipoprotein particles, the innate immune system may thus identify various endogenous signals that influence the immune response during the acute-phase reaction. The therapeutic emulsion intralipid also blocks LPC action on PPAR activity and DC maturation.Intralipid may thus be an alternative therapeutic strategy for some chronic inflammatory diseases.

Clin Nutr. 2003 Feb;22(1):59-64.

Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery.

Köller M, Senkal M, Kemen M, König W, Zumtobel V, Muhr G.

Source

Department of Surgery, BG Kliniken Bergmannsheil, Universitätsklinik, Bochum, Germany.

Abstract

Major surgery leads to post-traumatic immune dysregulation which is driven by the activation of potent proinflammatory mediators including the leukotrienes (LTs). The LTs of the four-series derive from arachidonic acid (an omega-6 fatty acid). In contrast, LTs of the five-series are metabolic products of eicosapentaenoic acid (an omega-3 fatty acid) and exert less biological activities. Therapeutical strategies to attenuate proinflammatory signals include the provision of omega-3 fatty acids. Thirty patients with major elective abdominal surgery and an indication for total parenteral nutrition (TPN) were compared in a prospective, double blind, randomized study of two parallel groups. Group 1 (n=14) received an omega-3 fatty acid enriched 20% lipid emulsion (MCT:LCT:fish oil = 5:4:1, MLF541; Lipoplus) for 5 days postoperatively. Group 2 (n=16) received a standard 20% fat emulsion (LCT; Intralipid). The LT release from whole blood leukocytes stimulated with Ca-ionophore was analyzed preoperatively and on postoperative days 1, 6 and 8 by HPLC. There was a significant increase in the generation of LTB(5) (P=0.0035) and in the ratio of LTB(5)/LTB(4) (P=0.0017)

the omega-3 group, but not in the reference group after 5 days infusion of the lipid emulsions. The omega-6/omega-3 fatty acid ratio 3:1 of the newly developed MLF541 lipid emulsion is appropriate to increase the synthesis of the biologically less active leukotrienes of the five-series. Nutritive enrichment with omega-3 fatty acids in a balanced ratio with omega-6 fatty acids is an important step to avoid hyperinflammatory situations in patients after major surgery.

J Immunol. 2002 Aug 15;169(4):1688-95.

Mature dendritic cell generation promoted by lysophosphatidylcholine.

Coutant F, Perrin-Cocon L, Agaugué S, Delair T, André P, Lotteau V.

Source

Centre d'Etude et de Recherche en Virologie et Immunologie, Institut National de la Santé et de la Recherche Médicale, Lyon, France. lotteau@cervi-lyon.inserm.fr

Abstract

During the acute phase response, the interplay between high density lipoproteins and low density lipoproteins (LDL) favors transient generation of oxidized LDL with proinflammatory activities. We hypothesized that oxidative modification of LDL is an endogenous signal for the immune system, and we have shown that oxidized LDL promotes mature dendritic cell transition from monocyte, therefore linking the nonspecific acute phase response to adaptive immunity. Lysophosphatidylcholine (LPC) is a major lipid component of oxidized LDL with reported proinflammatory activities. We now report that LPC acts through G protein-coupled receptors on differentiating monocytes to generate mature dendritic cells with the ability to stimulate IL-2 and IFN-gamma production by allogeneic T lymphocytes. LPC is most effective in lipoprotein-deprived serum and can be inhibited by an excess of native LDLs reflecting normal plasma conditions. Therefore, by controlling the balance between native and oxidized lipoproteins and the resulting production of LPC, the acute phase reactants may provide a context of Ag presentation that is transiently favorable to immune activation. Intralipid, a therapeutic lipid emulsion for parenteral nutrition with unexplained immunomodulatory properties, also blocked LPC activity. This opens perspectives for the understanding and treatment of acute and chronic inflammatory diseases.

Nutrition. 2002 Mar;18(3):235-40.

Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients.

Furukawa K, Yamamori H, Takagi K, Hayashi N, Suzuki R, Nakajima N, Tashiro T.

Source

First Department of Surgery, Chiba University School of Medicine, Japan. k-furukawa@umin.ac.jp

Abstract

OBJECTIVES:
We previously reported that omega-6 fat emulsion increases cytokine production in burned rats. Effects of soybean oil emulsion on surgical stress responses and lymphocyte function

according to the surgical severity have not been studied in detail. We investigated the effects of soybean oil emulsion, which contains 50% omega-6 fatty acid, on postoperative stress responses and cell-mediated immune function according to the severity of surgical stress.
METHODS:
Eight patients who underwent gastric or colorectal surgery and nine who underwent esophagectomy were fed fat-free total parenteral nutrition. Ten patients who underwent gastric or colorectal surgery and seven who underwent esophagectomy were fed total parenteral nutrition with soybean oil emulsion. Total parenteral nutrition provided 1.5 g of protein and 40 kcal per kilogram every day from 7 d before surgery to postoperative day 14. Soybean oil emulsion (Intralipid) accounted for 20% of the total calories. Serum interleukin-6, C-reactive protein, glucagon, and concanavalin A- or phytohemagglutinin-stimulated lymphocyte proliferation were determined.
RESULTS:
In the group of moderately stressed patients, soybean oil emulsion did not amplify the measured levels. In the group of severely stressed patients, soybean oil emulsion amplified the level of serum interleukin-6 and decreased concanavalin A- or phytohemagglutinin-stimulated lymphocyte proliferation.

CONCLUSIONS:
Soybean oil emulsion amplifies the stress responses and possibly suppresses cell-mediated immune function induced by surgical stress in severely stressed patients, but not in moderately stressed patients.

JPEN J Parenter Enteral Nutr. 2000 Nov-Dec;24(6):337-44.

Intralipid-based short-term total parenteral nutrition does not impair small intestinal mucosa-related cellular immune reactivity in the healthy rat.

Gross T, Babst R, Juretic A, Herzog B, Stehle P, Filgueira L, Oberholzer M, Gudat F, Heberer M.

Source

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Abstract

BACKGROUND:
The lipid component of total parenteral nutrition (TPN) has reportedly been associated with trophic effects on the intestinal mucosa and suppressive effects on the immunesystem.
METHODS:
We have challenged these hypotheses using a 7-day TPN rodent model comparing the effects of isocaloric, isonitrogenous lipid-based (TPN-lipid, 50% of calories as long-chain triacylglycerol) and carbohydrate-based TPN (TPN-CH, 100% of calories as carbohydrates) on mucosal morphology and immune function. Enterally fed animals were included to establish a baseline for immunologic read-outs. The study was performed in healthy, metabolically stable animals to avoid interference by septic or trauma-related stress factors.
RESULTS:
Both TPN regimens resulted in a significantly smaller weight gain (TPN-lipid, 29.8 +/- 4.0 g; TPN-CH, 30.3 +/- 4.4 g) compared with enterally fed reference animals (49.2 +/- 3.2 g; p = .007), with no difference in nitrogen balance between the TPN groups. Mucosal sucrase activity was significantly lower in both TPN groups (TPN-lipid, 8.8 +/- 1.0 x 10(-7) katal per gram (kat/g) of protein; CH: 11.9 +/- 1.6 x 10(-7) kat/g of protein) compared with enteral feeding (17.4 +/- 0.9 x 10(-7) kat/g of protein; ANOVA: p = .0007). Morphometric analysis of the small intestine revealed no differences between the two TPN groups although a

significantly depressed villus height in the TPN-lipid group could be observed in comparison to enterally fed reference rats (TPN-lipid, 0.47 +/- 0.02; TPN-CH, 0.50 +/- 0.01; enteral, 0.56 +/- 0.02 mm; ANOVA: p = .0298). Light and electron microscopy revealed a normal surface architecture in all three groups of rats. Cellular immunereactivity was evaluated using a novel specific immunization protocol: animals were immunized against OVA 4 weeks before TPN. OVA-induced lymphoproliferative responses and phenotypic data from draining popliteal and mesenteric lymph nodes were evaluated after the different regimens. Results did not differ among the three groups.

CONCLUSIONS:

In healthy rodents, short-term lipid-based and carbohydrate-based TPN regimens lead to limited mucosal atrophy with preserved surface architecture compared with enteral feeding. However, peripheral and mesenteric cellular immune responsiveness after both TPN regimens remained comparable to enterally fed reference animals. Therefore, mesenteric and systemic cellular immune reactivity does not appear to be impaired by lipid-based or carbohydrate-based TPN.

JPEN J Parenter Enteral Nutr. 2000 Mar-Apr;24(2):113-8.

Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro.

Granato D, Blum S, Rössle C, Le Boucher J, Malnoë A, Dutot G.

Source

Nestlé Research Center, Nestec LTD, Vers-chez-les-Blanc, Lausanne, Switzerland.

Abstract

BACKGROUND:

Numerous studies suggest that immune function may be compromised by lipid emulsions rich in polyunsaturated fatty acids (PUFAs). In our study, we compared the effect of a new olive oil-based lipid emulsion (ClinOleic) containing a moderate level of PUFAs, with emulsions based on soybean oil (Intralipid or Ivelip), on immune functions of human cell in vitro.

METHODS:

Peripheral white blood cells were collected from healthy volunteers. Lymphocyte proliferation was evaluated by [3H]-thymidine incorporation after stimulation with either phytohemagglutinin (PHA) or antibodies against T-cell specific antigens. Lymphocytes subsets and T-cell activation markers (CD25 and HLA-DR) were measured by flow cytometry. The release of cytokines (interleukin [IL]-2, IL-1beta, and tumor necrosis factor-alpha [TNF-alpha]) was measured by enzyme-linked immunosorbent assay (ELISA), after lymphocytes or monocytes/macrophages stimulation with PHA or lipopolysaccharide (LPS).

RESULTS:

A significant dose-dependent inhibition of thymidine incorporation was observed withIntralipid and Ivelip (incorporation down to 39.9% of control, p < .001) whereas ClinOleic showed no inhibitory effect. Activation antigen expression on both CD4+ and CD8+ T-cells tended to decrease with Intralipid (CD25: -53.4% on CD4+ and -57.4% on CD8+; HLA-DR: -61.5% on CD4+ and -58.5% on CD8+) but not with ClinOleic (from -2.9% for CD25 on CD4+ to 16.7% for HLA-DR on CD4+). Intralipid decreased significantly IL-2 production (-39.0%, p < .05) whereas ClinOleic had little effect (-13.0%, NS). Intralipid and ClinOleic tended to inhibit to a similar extent the release of pro-inflammatory cytokines (TNF-alpha: -21.5% and -34.8%, IL-1beta: -45.1% and -40.3%; respectively).

CONCLUSIONS:

Our results suggest that an olive oil-based lipid emulsion could modulateimmune response selectively, maintaining protective immunity and reducing inflammatory response. Olive oil may offer an immunologically neutral alternative to soybean oil for use in parenteral lipid emulsions.

Acta Anaesthesiol Scand. 1999 Jan;43(1):71-6.

Alterations of bacterial clearance induced by propofol.

Kelbel I, Koch T, Weber A, Schiefer HG, van Ackern K, Neuhof H.

Source

Department of Anaesthesiology, University of Ulm, FRG.

Abstract

BACKGROUND:
The purpose of the study was to investigate the potential influence of the anaesthetic agent propofol on immune function in terms of systemic clearance and organ distribution of injected Escherichia coli in a rabbit model.
METHODS:
Defined numbers of E. coli (1.3 x 10(8) colony-forming units, CFU) were injected intravenously 1 h after starting a 4-h infusion of the anaesthetic propofol (2 ml.kg-1.h-1, Disoprivan 1%; n = 6)) or after saline application (n = 6). As propofol is formulated in a 10% lipid emulsion, the lipid vehicle Intralipid (2 ml.kg-1.h-1; n = 6) alone was investigated in a separate group. Parameters monitored were arterial pressure and rates of bacterial elimination from the blood. Three hours after bacterial injection, the animals were killed, and tissue samples of liver, spleen, lung, and kidney were collected for microbiological examinations.
RESULTS:
Compared to saline-treated animals, infusion of propofol induced increased accumulation of E. coli in lung and spleen, thus reflecting reticuloendothelial system dysfunction.

CONCLUSION:
As the lipid emulsion by itself induced the same effects, the impaired immunefunction due to propofol is thought to be attributed to its solvent Intralipid.

Endocrinology. 1998 Dec;139(12):4811-9.

Hypothalamic mediated action of free fatty acid on growth hormone secretion in sheep.

Briard N, Rico-Gomez M, Guillaume V, Sauze N, Vuaroqueaux V, Dadoun F, Le Bouc Y, Oliver C, Dutour A.

Source

Laboratoire des Intéractions Fonctionnelles en Neuroendocrinologie, INSERM U-501, Institut Fédératif Jean Roche, Marseille, France.

Abstract

Experimental data suggest that elevated FFA levels play a leading role in the impaired GH secretion in obesity and may therefore contribute to the maintenance of overweight. GH has a

direct lipolytic effect on adipose tissue; in turn, FFA elevation markedly reduces GH secretion. This suggests the existence of a classical endocrine feedback loop between FFA and GH secretion. However, the FFA mechanism of action is not yet understood. The involvement of somatostatin (SRIH) is controversial, and in vitro experiments suggest a direct effect of FFA on the pituitary. In sheep it is possible to collect hypophysial portal blood and quantify SRIH secretion in hypophysial portal blood under physiological conscious and unstressed conditions. In this study we determined the effects of FFA (Intralipid and heparin) infusion on peripheral GH and portal SRIH levels in intact rams chronically implanted with perihypophysial cannula and in rams actively immunized against SRIH to further determine SRIH-mediated FFA effects on GH axis. Immediately after initiation of Intralipid infusion, we observed a marked increase in the FFA concentration (2160 +/- 200 vs. 295 +/- 28 nmol/ml; $P < 0.01$) as well as a significant decrease in basal GH secretion (1.8 +/- 0.1 vs. 2.5 +/- 0.3 ng/ml; $P < 0.05$) and a drastic reduction of the GH response to i.v. GH-releasing hormone injection (4.8 +/- 0.7 ng/ml in FFA group vs. 35.8 +/- 9.7 ng/ml in saline group; $P < 0.01$). No change in plasma insulin-like growth factor I levels was observed. During the first 2 h of infusion, the GH decrease observed was concomitant with a significant increase in portal SRIH levels (22.1 +/- .2 vs. 13 +/- 1.6 pg/ml; $P < 0.01$). In rams actively immunized against SRIH, the effect of FFA on basal GH secretion was biphasic. During the first 90 min of infusion, the decrease in GH induced by FFA was significantly blunted in rams actively immunized against SRIH (57 +/- 9% for immunized rams vs. 23.5 +/- 2.5% for control rams). This corresponds to the period of increased SRIH portal levels. After this first 90-min period, no difference was seen between control and immunized rams. Our results show that FFA exert their inhibitory action on the GH axis at both pituitary and hypothalamic levels, the latter mainly during the first 90 min, through increased SRIH secretion.

Acta Paediatr. 1997 Apr;86(4):410-3.

Effect of lipid emulsion on IL-2 production by mononuclear cells of newborn infants and adults.

Sirota L, Straussberg R, Notti I, Bessler H.

Source

Neonatology Unit, Sackler School of Medicine, Tel Aviv University, Israel.

Abstract

The in vitro effect of a lipid emulsion (intralipid) on interleukin-2 (IL-2) production by cord blood mononuclear cells (CBMC) of preterm and term newborn infants was examined and compared to that of peripheral blood mononuclear cells (PBMC) of adults. Intralipid, added at concentrations accepted in clinical practice, caused a dose-dependent inhibition of IL-2 activity tested by bioassay. IL-2 levels, tested by radioimmunoassay (RIA), were found to be reduced only in supernatants derived from CBMC of term infants and not in those derived from MC of preterm infants or adults. The capacity of the IL-2 dependent cell line CTLL-2 to respond to IL-2 was abolished in the presence of intralipid, suggesting an interference with the binding of IL-2 to its receptor on these cells. It is conceivable that administration of intralipid to preterm infants may interfere with the binding of IL-2 to the specific receptors on their activated lymphocytes, with a possible subsequent suppression of their immune response.

Anaesthesia. 1997 Apr;52(4):341-4.

Effects of propofol emulsion and thiopentone on T helper cell type-1/type-2 balance in vitro.

Salo M, Pirttikangas CO, Pulkki K.

Source

Department of Anaesthesiology, Turku University Central Hospital, Finland.

Abstract

We have earlier found increased percentages of T helper cells (CD4-positive lymphocytes) in the blood circulation after propofol infusion anaesthesia. Cytokines interferon-gamma (IFN gamma) and interleukin-4 (IL-4) are important in the differentiation of T helper cells into subtypes T helper type-1 (Th1) and type-2 (Th2). To study the effects of propofol emulsion, its solvent Intralipid and thiopentone on Th1/Th2 balance, measurements of IFN gamma and IL-4 production by mononuclear leucocytes were carried out in vitro. As IL-2 has a central role in immune responses to surgery, its production was also measured. Concanavalin A-stimulated mononuclear cells were cultured in the presence of propofol emulsion at 3.5 or 10 micrograms.ml-1, Intralipid 35 or 100 micrograms.ml-1, or thiopentone 3 micrograms.ml-1. Cytokine production was measured from the conditioned media of mononuclear cell cultures. Decreased IFN gamma ($p < 0.001$) and IL-4 concentrations ($p < 0.01$) were found in the presence of thiopentone, but IL-2 production was unaffected. By contrast, propofol emulsion or Intralipid had no effects on IFN gamma, IL-2 or IL-4 concentrations. Propofol 10 micrograms.ml-1 increased the IFN gamma/IL-4 ratio from the control value median 243 (162-562) (25th-75th percentile) to 363 (195-1028) ($p < 0.01$), but thiopentone decreased it to 145 (60-214) ($p < 0.01$). These findings show that propofol and thiopentone have different effects in vitro on Th1/Th2 balance and suggest that they have different modulating effects on the immune response.

Biochim Biophys Acta. 1996 Jun 11;1301(3):221-9.

Quantitation of apolipoprotein B-48 in triacylglycerol-rich lipoproteins by a specific enzyme-linked immunosorbent assay.

Lovegrove JA, Isherwood SG, Jackson KG, Williams CM, Gould BJ.

Source

Centre for Nutrition and Food Safety, School of Biological Sciences, University of Surrey, Guildford, UK.

Abstract

This paper describes the use of an antiserum, specific for apolipoprotein (apo) B-48, in a competitive, enzyme-linked immunosorbent assay (ELISA) for apo B-48 in triacylglycerol-rich lipoprotein (TRL) fractions prepared from fasting and post-prandial plasma samples. Previously we showed the antiserum to act as an effective immunoblotting agent following sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Its use in this ELISA indicates that the antiserum recognises the C-terminal region of the protein on the surface of lipoprotein particles. The ELISA had a sensitivity of less than 37 ng/ml and intra- and inter-assay coefficients of variation of 3.8% and 8.6%, respectively. There was no cross-reaction in the ELISA against serum albumin, ovalbumin, thyroglobulin, or apo B-100 (purified by immunoaffinity chromatography), and high lipid concentrations (as Intralipid) did not interfere. A low density lipoprotein fraction reacted in the ELISA but SDS-PAGE-Western blot analysis confirmed the presence, in the fraction, of a small amount of apo B-48, indicating the

existence of low density dietary-derived lipoprotein particles. ELISA and SDS-PAGE-Western blot analysis were used to measure apo B-48 in 12 series of postprandial samples collected from 4 diabetic and 8 normal subjects, following test meals of varying fat content. The mean correlation between the two methods was r = 0.74. The mean fasting concentration of apo B-48 in the TRL fractions from 15 healthy men was 0.46 microgram/ml of plasma.

Anaesthesia. 1995 Apr;50(4):317-21.

Effects of propofol and Intralipid on immune response and prostaglandin E2 production.

Pirttikangas CO, Salo M, Riutta A, Perttilä J, Peltola O, Kirvela O.

Source

Department of Anaesthesiology, University of Turku, Finland.

Abstract

The present study evaluated the effects of propofol and its solvent Intralipid on the immuneresponse and in vivo prostaglandin E2 production in patients during induction of anaesthesia and in healthy volunteers after Intralipid injection. Fifteen female patients (median age 48 years, ASA 1-2) scheduled for uterine dilatation and curettage were randomly assigned to two groups. In group 1 propofol (median dose 3.1 mg.kg-1) and in group 2 thiopentone (median dose 6.0 mg.kg-1) were injected intravenously over 60 s. Surgery was started after collection of the last blood sample. In the second part of this study, Intralipid 10% 0.3 ml.kg-1 was injected intravenously in eight healthy volunteers (four women and four men, median age 32 years) over 60 s. Plasma bicyclo-PGE2 concentrations increased during anaesthesia induction in both anaesthetic groups ($p < 0.01$). By contrast, no changes were seen in plasma bicyclo-PGE2 concentrations after Intralipid injection in volunteers. Lymphocyte proliferative responses to mitogens did not change during anaesthesia induction in patients. In volunteers, Intralipid injection caused a slight increase in T-cell percentages ($p < 0.01$) and unstimulated lymphocyte proliferative responses ($p < 0.05$), but it did not affect other lymphocyte subsets and immunoglobulin production. Intralipid and propofol were not found to be immunosuppressive at clinical doses used during anaesthesia induction.

Mediators Inflamm. 1993;2(7):S29-32.

L-carnitine: a partner between immune response and lipid metabolism ?

Famularo G, Tzantzoglou S, Santini G, Trinchieri V, Moretti S, Koverech A, De Simone C.

Source

Department of Internal Medicine and Public Health Via S. Sisto University of L'Aquila 67100 Italy.

Abstract

The authors demonstrated that in vivo administered L-carnitine strongly ameliorated the immuneresponse in both healthy individuals receiving Intralipid and ageing subjects with cardiovascular diseases, as shown by the enhancement of mixed lymphocyte reaction. Notably, in the latter group L-carnitine treatment also resulted in a significant reduction of serum levels of both cholesterol and triglycerides. Therefore, the hypothesis is that L-carnitine supplementation could ameliorate both the dysregulated immune response and the abnormal lipid metabolism in several conditions.

Br J Anaesth. 1992 Jul;69(1):70-4.

Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization in vitro in the presence or absence of human serum albumin.

O'Donnell NG, McSharry CP, Wilkinson PC, Asbury AJ.

Source

University Department of Anaesthesia, Western Infirmary, Glasgow.

Abstract

Anaesthetic agents inhibit some aspects of immune function and this may be clinically important when prolonged infusions are used in an intensive care unit. We have studied the effects of propofol, thiopentone and midazolam on neutrophil polarization in vitro. At concentrations seen in plasma during anaesthesia, propofol and thiopentone produced significant (approximately 50%) and comparable degrees of inhibition. Inhibition was complete with greater concentrations of these drugs. When compared with equivalent concentrations of midazolam, propofol produced more inhibition (P less than 0.01) at all concentrations investigated, except the smallest. Midazolam produced no effect at clinically relevant concentrations. The effect of propofol was not attributable to its lipid carrier vehicle, as 10% Intralipid alone augmented neutrophil polarization. Human serum albumin conferred some degree of protection against the inhibition produced by clinically relevant concentrations of propofol and thiopentone, but not that produced by greater concentrations of these drugs.

JPEN J Parenter Enteral Nutr. 1992 Mar-Apr;16(2):165-7.

Clinical and immunologic effects of lipid-based parenteral nutrition in AIDS.

Singer P, Rubinstein A, Askanazi J, Calvelli T, Lazarus T, Kirvelä O, Katz DP.

Source

Department of Anesthesiology, Montefiore Medical Center, Bronx, NY 10467.

Abstract

The effect of lipid-based parenteral nutrition was assessed in eight patients with AIDS and weight loss of 10% or greater. All patients received home parenteral nutrition consisting of a lipid-based system with 50% of nonprotein calories given as fat. Measurements were made of body weight, serum albumin, and immune function as assessed by mitogen responses, P24 antigen levels and T-cell counts. Over a period of 2 months, weight gain and improved well-being were noted in all patients. An improved in vitro lymphocyte mitogenic response to phytohemagglutinin and to concanavalin A was also noted. No change in T-cell subsets was observed. Viral cultures and P24 serum levels also remained unchanged. Lipid-based parenteral nutrition is safe and probably efficacious in AIDS.

Zhonghua Wai Ke Za Zhi. 1990 Dec;28(12):739-41, 782.

[Effects of perioperative parenteral nutrition on immunocompetence in patients with gastric cancer].

[Article in Chinese]

Yan M.

Source

Ruijin Hospital, Shanghai Second Medical University.

Abstract

To elucidate the effects of parenteral nutrition on the immunocompetence, we administrated parenteral nutritional support to the malnourished gastric cancer patients during perioperative periods. Changes of peripheral blood natural killer cytotoxicity (NKC) activity (LDH enzyme-release assay) and T lymphocyte subsets (OKT series monoclone antibody indirect fluorescent assay) were monitored before and after nutritional support. The results showed that one week of pre or postoperative parenteral nutrition significantly increased the NKC activity, T-helper, and T-helper/T-suppressor ratio. The total T lymphocytes count may also increase. T-suppressors remained unchanged no matter whether nutritional support was given or not. The authors believe that perioperative nutritional support could improve the immunocompetence of gastric cancer patients to some extent, and promote the restoration of immune depression caused by operation, but it could not eliminate the effects of immune depressing factor produced by the tumor. Intralipid can be used properly as non protein energy source without immunodepressing effects.

JPEN J Parenter Enteral Nutr. 1990 Sep-Oct;14(5):459-62.

Inhibition of immunoglobulin synthesis in vitro by intravenous lipid emulsion (Intralipid).

Salo M.

Source

Department of Anaesthesiology, University of Turku, Finland.

Abstract

Intravenous lipid emulsions depress lymphocyte proliferative responses and granulocyte function at concentrations found in the blood circulation during their administration. The effects of Intralipid, a widely used intravenous lipid emulsion, were measured on immunoglobulin production in vitro by pokeweed mitogen-activated lymphocytes as a test of B-cell function. Intralipid decreased IgG, IgM, and IgA production at soybean oil triglyceride concentrations of 2.5-20 mg/ml occurring in the blood circulation during Intralipid infusion. The effects on IgM and IgA production were highest and that on IgG production lowest. Hydrocortisone-sensitive and concanavalin A-inducible suppressor cells were more sensitive to Intralipid than other cell populations. In vivo Ig production may not be equally disturbed, inasmuch as Intralipid concentrations in the lymph nodes and the spleen may be lower than in the blood circulation. However, care should be taken to prevent Intralipidconcentrations from becoming high enough to depress immune responses.

Vaccine. 1989 Feb;7(1):39-48.

Enhancement of humoral immune responses against viral vaccines by a non-pyrogenic 6-O-acylmuramyldipeptide and synthetic low toxicity analogues of lipid A.

Tsujimoto M, Kotani S, Okunaga T, Kubo T, Takada H, Kubo T, Shiba T, Kusumoto S, Takahashi T, Goto Y, et al.

Source

Department of Microbiology and Oral Microbiology, Osaka University Dental School, Japan.

Abstract

6-O-Acyl derivatives of N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP) and synthetic, low toxicity lipid-A analogues were examined for their ability to enhance the potency of current viral vaccines. 6-O-(2-Tetradecylhexadecanoyl)-MDP (B30-MDP) in non-irritative vehicles such as physiological saline, phosphate-buffered saline (PBS), squalene-PBS emulsion, Intralipid or liposomes, significantly stimulated the primary and secondary antibody production of guinea-pigs against influenza split or subunit vaccine and inactivated the hepatitis B virus surface (HBs) antigen. Mice seemed less responsive to the adjuvanticity of B30-MDP than guinea-pigs. Two low toxicity lipid A analogues, acylated beta(1-6)-D-glucosamine disaccharide bisphosphates (which do not have amide-bound or ester-bound 3-acyloxyacyl groups unlike fully toxic Escherichia coli-type lipid A), caused significantly enhanced antibody responses, primary or secondary, when administered to mice by incorporation into liposomes with inactivated HBs antigen.

Scand J Gastroenterol Suppl. 1988;143:1-4.

Relation between defective regulation of arachidonic acid release and symptoms in cystic fibrosis.

Strandvik B, Brönnegård M, Gilljam H, Carlstedt-Duke J.

Source

Dept. of Pediatrics, Karolinska Institutet, Huddinge University Hospital, Sweden.

Abstract

A hypothesis is formed about the basic defect in CF based on the findings of 1) a defective inhibition of AA release by dexamethasone stimulation of lymphocytes from patients with CF, probably due to a defect in or absence of lipocortin and 2) the essential fatty acid deficiency (EFAD) in CF reported by different authors for 25 years. Both in lymphocytes and fibroblasts from patients with CF increased AA release has been demonstrated. AA, substrate for the eicosanoid system (prostaglandins, leukotrienes, hydroxyeicosatetraenoic acids, thromboxanes), has been shown to increase mucus release, influence chloride transport and the stimulus-secretion coupling (Ca++ balance), all factors suggested as basic defects in CF. The increased release of AA might explain the development of EFAD, since AA is synthesized from linoleic acid. In animals EFAD gives rise to symptoms similar to those in CF, e.g. defect Na transport, liver steatosis, increased caloric need, disturbed insulin release, increased bacterial colonization of airways, and decreasedimmune response. Regular supplementation with fat emulsion (Intralipid) to CF patients normalizes the renal Na transport and prevents liver steatosis. We suggest that the basic defect in CF is a defect in or absence of lipocortin, causing an increased release of AA, which regulates synthesis in the eicosanoid system. An increase of the products in this system gives rise to the basic signs and symptoms

of CF. The resulting EFAD is dependent on the rate of AA turnover and could explain most of the clinical symptoms and the progression of the disease.

Br J Surg. 1986 Oct;73(10):843-6.

Immunorestorative effect of lipid emulsions during total parenteral nutrition.

Monson JR, Ramsden CW, MacFie J, Brennan TG, Guillou PJ.

Abstract

This prospective in vivo cross-over study investigated the effect of Intralipid on immune responses. Twenty-three patients were randomly allocated to receive one of two alternative total parenteral nutrition (TPN) regimens for the first 7 days and the other regimen for the second 7 days. Only one of the regimens included a fat emulsion to provide 50 per cent of the calorific requirement. Immunological studies were performed on days 0, 7 and 14. These included peripheral blood T cell subsets, antibody dependent cellular cytotoxicity and basal and maximal Interleukin 2 production. All immunological parameters were significantly augmented during total parenteral nutrition using the lipid based regimen. No such change was seen during intravenous feeding with carbohydrate based TPN. It is concluded that, far from being immunosuppressive, the incorporation of a fat emulsion into a TPN regimen has immunostimulatory properties.

Infect Immun. 1986 Sep;53(3):517-21.

Adjuvant activity of 6-O-acyl-muramyldipeptides to enhance primary cellular and humoral immune responses in guinea pigs: dose-response and local reactions observed with selected compounds.

Tsujimoto M, Kotani S, Shiba T, Kusumoto S.

Abstract

6-O-(2-Tetradecylhexadecanoyl)-N-acetylmuramyl-L-alanyl-D-isoglutamine (B3O-MDP) and 6-O-(3-hydroxy-2-docosylhexacosanoyl)-MDP (BH48-MDP) were examined for immunopotentiating activity in stimulating the primary immune responses of guinea pigs to ovalbumin and for adverse reactions at the injection site and in the regional lymph nodes when administered in combination with several nonirritating vehicles. B30-MDP was found to potently stimulate both humoral and cellular immune responses, the latter by induction of delayed-type hypersensitivity, irrespective of the administration vehicle examined (liposomes, a squalene in water emulsion, Intralipid, phosphate-buffered saline, and Nikkol HCO-60 glucose solution), although the minimum effective dose was dependent on the vehicle used. Reactions in the footpad receiving the injection were negligible. Noticeable local reaction consisted of swelling of the lymph nodes in the region of the injection, but the swelling was only noted with higher doses and subsided 3 to 4 weeks after immunization, unlike the persistent swelling caused by the administration of water-in-mineral oil emulsions with or without B30-MDP. BH48-MDP and its L-serine analog, BH48-MDP(L-Ser), which has L-serine in place of L-alanine in MDP, in combination with the squalene-in-water emulsion, also intensely stimulated both cellular and humoral antiovalbumin immune responses, but the effects of these compounds seemed to be influenced to a greater degree by the vehicles than by B30-MDP. Thus, B30-MDP was chosen from a series of a 6-O-acyl derivatives of MDP as the most promising candidate for possible application in practical vaccines

Biochim Biophys Acta. 1985 Dec 4;837(3):262-70.

Distribution of lipoprotein lipase and hepatic lipase between plasma and tissues: effect of hypertriglyceridemia.

Peterson J, Olivecrona T, Bengtsson-Olivecrona G.

Abstract

Lipoprotein lipase and hepatic lipase were measured in rat plasma using specific antisera. Mean values for lipoprotein lipase in adult rats were 1.8-3.6 mU/ml, depending on sex and nutritional state. Values for hepatic lipase were about three times higher. Lipoprotein lipase activity in plasma of newborn rats was 2-4-times higher than in adults. In contrast, hepatic lipase activity was lower in newborn than in adult rats. Following functional hepatectomy there was a progressive increase in lipoprotein lipase activity in plasma, indicating that transport of the enzyme from peripheral tissues to the liver normally takes place. Lipoprotein lipase, but not hepatic lipase, increased in plasma after a fat meal. An even more marked increase, up to 30 mU/ml, was seen after intravenous injection of Intralipid. Plasma lipase activity decreased in parallel with clearing of the injected triacylglycerol. 125I-labeled lipoprotein lipase injected intravenously during the hyperlipemia disappeared somewhat slower from the circulation than in fasted rats, but the uptake was still primarily in the liver. Hyperlipemia, or injection of heparin, led to increased lipoprotein lipase activity in the liver. This was seen even when the animals had been pretreated with cycloheximide to inhibit synthesis of new enzyme protein. These results suggest that during hypertriglyceridemia lipoprotein lipase binds to circulating lipoproteins/lipid droplets which results in increased plasma levels of the enzyme and increased transport to the liver.

Clin Nutr. 1985 Nov;4(4):229-34.

Effect of Intralipid on some immunological parameters and leukocyte functions in patients with esophageal and gastric cancer.

Dionigi P, Dionigi R, Prati U, Pavesi F, Jemos V, Nazari S.

Source

Dipartimento di Chirurgia, Sezione di Patologia Chirurgica, Università di Pavia Pavia, Italy.

Abstract

This study has been undertaken to investigate if the intravenous (i.v.) infusion of fat emulsions may be associated with impairment of some immunological functions thus increasing the risk of septic complications. Fifteen malnourished patients with advanced gastric or esophageal cancer received for 2 weeks preoperatively and 1 week after surgery an isocaloric and isonitrogenous TPN treatment with Intralipid (group A: n=8) or glucose alone (group B: n=7) as energy substrate. Cluster analysis of 11 nutritional parameters and some tests of the humoral and cellular immunity (IgG, IgM, C3c, Factor B; polymorphonuclear (PMN) cells, total lymphocytes, T and B lymphocyte counts; 'in vitro' PMN chemotaxis, adherence to nylon fibers, phagocytosis of latex particles) were sequentially determined. The incidence and severity of post-operative infections were investigated and a 'sepsis score' was calculated for each patient. Pre- and postoperative TPN were not associated with an improvement of the nutritional status. The humoral and cellular immuneparameters showed the same behaviour

in patients receiving Intralipid and in controls. The chemotactic activity of PMN cells was constantly normal, granulocyte adherence fluctuated below the normality range in controls, whereas phagocytosis of latex was similar in both groups. Post-operative infectious episodes were less severe in patients receiving Intralipid. Our results do not confirm that Intralipid adversely affects some aspects of the humoral and cellular immuneresponse.

Clin Nutr. 1985 Aug;4(3):175-8.

The effect of preoperative nutrition on the immune system.

Rasmussen A, Segel E, Trier Aagaard M, Hessov I.

Source

Dept. of Clinical Haematology and Medicine, Aarhus amtssygehus, 8000 Arhus C, Denmark.

Abstract

In many surgical departments it has been common practice to give patients with weight loss pre-operative parenteral nutrition before major surgery. The purpose of the present study was to elucidate the value of intravenous pre-operative nutrition in relation to the immune system. The study comprised 10 patients undergoing total gastrectomy. All patients had a weight loss of 15% of body weight or more within 6 months or 10% within 3 months. Before operation they all received parenteral nutrition for 1 week. They all had 1.5 g of protein per kg per day and energy corresponding to the basal metabolic rate + 50% as Vamin, Intralipid, and carbohydrate solutions. Before and after this treatment blood samples were taken to estimate neutrophil function (the rate of oxygen consumption and superoxide liberation, phagocytosis and intracellular lysis of Candida albicans, the concentration and consumption rate of ATP during phagocytosis, and chemotaxis) and immune globulins (IgG, IgM, & IgA). Cellular immunity (CMI) was estimated by intradermal application of seven different antigens. We found a significant increase in response to the intradermal antigens ($p < 0.01$) but no difference in any of the parameters expressing leukocyte function or immune globulins.

JPEN J Parenter Enteral Nutr. 1985 Jan-Feb;9(1):23-7.

Immune function during intravenous administration of a soybean oil emulsion.

Ota DM, Jessup JM, Babcock GF, Kirschbaum L, Mountain CF, McMurtrey MJ, Copeland EM 3rd.

Abstract

The effect of a continuous infusion of a soybean oil emulsion on immune function was evaluated in 40 malnourished patients who were randomized to receive preoperatively either a 25% glucose-5% amino acid solution (group G) or a 15% glucose-3.3% Intralipid-5% amino acid solution (group G-F). Average length of total parenteral nutrition (TPN) was 10.3 +/- 0.9 days for group G and 9.0 +/- 0.8 days for group G-F. Initial nutritional status and response to TPN were similar for both groups.Immune function was assessed before TPN and after nutritional repletion prior to surgery for each patient. The levels of immunoglobulins, C3, C4, circulating B lymphocytes and T lymphocytes, suppressor T lymphocytes, natural killer cell activity, and monocytes were normal before TPN and after nutritional therapy. However, the total number of T cells and helper T cells were low before TPN and remained so after TPN. In addition, lymphocyte function measured by the lymphocyte blastogenic response to phytohemagglutinin and pokeweed mitogen was depressed prior to TPN and was not improved by either regimen. Neutrophil chemotaxis and bactericidal activity were not affected by either nutritional regimen while neutrophil phagocytosis was enhanced before TPN and

remained elevated throughout TPN with either regimen. There were no differences in infection rates during TPN. The addition of Intralipid to the TPN regimen did not alter immune function in these patients who showed depressed cell-mediated immunity before TPN compared with the standard glucose TPN regimen.

JPEN J Parenter Enteral Nutr. 1984 Jul-Aug;8(4):381-4.

The effects of intralipid and heparin on human monocyte and lymphocyte function.

Fraser I, Neoptolemos J, Darby H, Bell PR.

Abstract

A group of patients were studied during the infusion of Intralipid as part of a parenteral nutrition regimen. Peripheral blood lymphocyte function was unaffected, but monocyte function (chemotaxis) was significantly depressed. A group of healthy volunteers received an intravenous bolus of 20% Intralipid. Blood was taken before and 15 min afterward for immunological studies, and the same changes were seen following Intralipid. Prior subcutaneous injection of 5000 U of heparin did not affect either immunological parameter, but completely prevented the changes in monocyte function caused by Intralipid. Electronmicrographs of monocytes from volunteers after injection of Intralipid, and autoradiographs of cells incubated with 14C-Intralipid in vitro, showed phagocytosis of fat particles by monocytes. These data suggest that Intralipid can have potentially serious side effects on the immune system, and that they may be alleviated by the use of subcutaneous heparin.

JAMA. 1984 Mar 23-30;251(12):1574-9.

Parenteral fat emulsions and immune adherence. The effects of triglycerides on red cell and neutrophil immune adherence in vitro and in vivo.

Siegel I, Liu TL, Zaret P, Gleicher N.

Abstract

Parenteral fat emulsions may not only exert nutritional effects but may also affect immuneadherence phenomena and red cell morphology. Red cell immune adherence (RCIA) was augmented in vitro by 0.05% to 0.1% Intralipid. Similar augmentation of RCIA was observed by peanut oil, corn oil, half-and-half cream, paraffin oil, and human low-density lipoprotein fractions. Neutrophil immune adherence was augmented in vitro by 0.2% to 1.5% of Intralipid. The effects of fat emulsions in vivo were studied in ten patients who received intralipid for nutritional purposes. Red cell immune adherence was augmented in five of ten patients and inhibited in four of ten patients. Neutrophil immune adherence was augmented in two of ten patients. Cytotoxic red cell transformations were evident in five of ten patients. Depression of RCIA in four of five patients was associated with cytotoxic red cell transformations.

Arzneimittelforschung. 1982;32(11):1485-8.

Reversibility by L-carnitine of immunosuppression induced by an emulsion of soya bean oil, glycerol and egg lecithin.

De Simone C, Ferrari M, Meli D, Midiri G, Sorice F.

Abstract

Experimental and clinical data appear to indicate that Intralipid--an emulsion of soya bean oil, glycerol and egg lecithin--which is usually employed to improve caloric intake of parenteral nutrition regimens, may compromise human host defence mechanisms and therefore expose patients to an increased incidence of infectious diseases. Since from a biochemical point of view it has been suggested that a possible way whereby the somewhat poor reputation of Intralipid--attributable to the liver damage and the persistent lipaemia which attend its use--might be improved is to give supplementary carnitine which acts as a rate-limiting factor in the removal of the fat emulsion from blood, we hypothesized that the addition of carnitine to Intralipid could also result in a improvement of the immune responses both "in vitro" and "in vivo". Our results lend some support to the hypothesis in favour of a metabolic basis for some of the immunosuppressive properties of Intralipidand justify the inclusion of L-carnitine in parenteral nutrition regimens which, by abrogating some co-factor limitation, improves the immune responses of the host.

Acta Chir Belg. 1981 Mar-Jun;80(2-3):149-55.

Influence of total parenteral nutrition (TPN) on some immuneparameters in malnourished surgical patients.

Carpentier YA, Druart ML, Delespesse G.

Abstract

Twenty-one protein-calorie depleted patients were given for one week total parenteral nutrition (TPN) including Intralipid during a sixteen months' period (September 1975 - December 1976). Before TPN, lymphocyte proliferation response to 1 microgram/ml of phytohemagglutinin (PHA) was abnormally low, while immunoglobulin levels were in the normal range. After one week of TPN, lymphocyte response to PHA was significantly improved in patients exhibiting positive nitrogen balance but remained unchanged in the others. Immunoglobulin IgA, IGG, IgM levels tended to rise in most of the patients, while IgE concentrations remained unchanged. Addition of Intralipid at various concentrations to lymphocyte cultures of both patients and normal volunteers did not effect 3H-thymidine incorporation in the lymphocytes. Similarly, in vivo infusion of Intralipid in normal subjects did not have any effect on lymphocyte performance. This study shows that: 1. effective TPN can correct some alterations in immune parameters; 2. Intralipid does not seem to have any effect on the parameters measured in the present work.