Clinical Nutrition 34 (2015) 400–408

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Incorporation and washout of n-3 PUFA after high dose intravenous and oral supplementation in healthy volunteers

Frederik Delodder [a], Luc Tappy [b], Lucas Liaudet [a], Philippe Schneiter [b], Christian Perrudet [a, c], Mette M. Berger [a, *]

[a] Service of Adult Intensive Care Medicine, University Hospital (CHUV), Lausanne, Switzerland
[b] University Physiology Institute, University of Lausanne, Lausanne, Switzerland
[c] Institute of Life Science, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 18 January 2014
Accepted 1 July 2014

Keywords:
Membrane incorporation
Lactate
Platelet function
Pharmacokinetic
Fish oil

SUMMARY

Background & aims: Although the physiological effects of n-3 polyunsaturated fatty acids (n-3PUFA) are generally thought to require several weeks of exposure to allow their incorporation into plasma membranes, intravenous (IV) n-3PUFA attenuate the cardiovascular and neuroendocrine response to stress within 3 h. Whether oral n-3 PUFA exert similar early effects remains unknown.
Objective: To assess whether acute IV or short term oral n-3PUFA administration reproduces the metabolic effects of long term oral supplements during exercise, and how it relates to their incorporation into platelets and red blood cells (RBC) membranes.
Design: Prospective single center open label study in 8 healthy subjects receiving a 3-h infusion of 0.6 g/kg body weight n-3PUFA emulsion, followed one week later by an oral administration of 0.6 g/kg over 3 consecutive days. Maximal power output (cycling exercise), maximal heart rate (HR), blood lactate at exhaustion, and platelet function were measured at baseline and after IV or 3-day oral supplementation; platelet and RBC membrane composition were assessed until 15 days after n-3PUFA administration.
Results: Both IV and oral n-3PUFA significantly decreased maximal HR (-6% and -5%), maximal power output (-10%) and peak blood lactate (-47% and -52%) Platelet function tests were unchanged. The EPA and DHA membrane contents of RBC and platelets increased significantly, but only to 1.7-1.9% of fatty acid content.
Conclusion: The cardiovascular and metabolic effects of n-3 PUFA during exercise occur already within 1–3 days of exposure, and may be unrelated to changes in membranes composition. Effects occur within hours of administration and are unrelated to lipid membrane composition.
Trial registered at clinicaltrials.gov as NCT00516178.

1. Introduction

Due to their potential to reduce mortality in coronary disease [1] n-3 polyunsaturated fatty acids (n-3 PUFA) have generated a large body of research. The long chain n-3 PUFA, such as eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) found in fish oil, modulate the inflammatory processes by decreasing the synthesis of inflammatory prostaglandins and eicosanoid, by inducing the synthesis of anti-inflammatory resolvins, and by regulating the expression of inflammatory genes [2]. They also modulate cardiovascular and metabolic responses to stress and diseases [3]. These effects are thought to require an incorporation of n-3 PUFA into plasma membranes of target tissues [4].

It is generally assumed that the beneficial effects of oral n-3 PUFA develop over several weeks. Few studies have addressed their time-course or their kinetics for incorporation into plasma membranes however. We have recently observed significant n-3 PUFA incorporation into both platelets and RBC membranes and relevant anti-inflammatory effects in response to an endotoxin challenge within 1–2 days after intravenous (IV) administration [5–7]. This contrasts with the common belief that several weeks of oral n-3

* Corresponding author. Service of Adult Intensive Care Medicine & Burns, Lausanne University Hospital (CHUV BH-08.612), Rue du Bugnon 46, CH – 1011 Lausanne, Switzerland. Tel.: +41 21 31 42 095; fax: +41 21 31 43 045.
E-mail addresses: fdelodder@gmail.com (F. Delodder), luc.tappy@unil.ch (L. Tappy), Lucas.Liaudet@chuv.ch (L. Liaudet), Philippe.Schneiter@unil.ch (P. Schneiter), perrudet@gmail.com (C. Perrudet), Mette.Berger@chuv.ch (M.M. Berger).
URL: http://www.soins-intensifs.chuv.ch

http://dx.doi.org/10.1016/j.clnu.2014.07.005
0261-5614/

Abbreviations

EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
FA	fatty acid
FO	fish oil
ICU	intensive care unit
NEFA	non esterified fatty acids
n-3	omega 3
PUFA	polyunsaturated fatty acids
RBC	red blood cell
TG	plasma triglycerides

PUFA supplementation are required to achieve membrane incorporation and physiological effects [8–10].

To our knowledge, no study has assessed whether oral n-3 PUFA supplementation exerts early, very short term physiological effects as IV administration does. To address this question, we have measured heart rate and blood lactate responses to a maximal incremental cycling exercise in healthy subjects [11]. We selected this specific outcome because we have recently shown that heart rate and blood lactate were significantly reduced after a 4-week oral n-3 PUFA in healthy subjects, and have shown that high dose perioperative intravenous n-3 PUFA modified cardiac tissue composition in coronary bypass patients [7]; in this regard, n-3 PUFA are known to reduce heart rate and heart rate variability in cardiac surgery patients [12].

N-3 PUFA-induced changes in platelet and RBC membrane composition were measured using a commercially available n-3 PUFA determination method. We also assessed the effects of short-term high dose n-3 PUFA supplements on platelet function and primary hemostasis.

2. Subjects and methods

This pilot study was designed as a single center open label pharmacokinetic study. The study endpoints were 1) kinetics of the PUFA membrane composition in response to oral and IV n-3 PUFA supplementation, and 2) heart rate changes and blood lactate concentration during exercise, platelet activation.

The study was approved by the Ethical Committee of the Canton de Vaud, and the Swiss Agency for therapeutic Products (Swissmedic No2007DR3297), and was registered on ClinicalTrials.gov (NCT00516178).

2.1. Subjects

The eligibility to the study was conditioned by the results of a preliminary visit to the laboratory including a complete negative medical history, a physical examination, a 12-lead electrocardiogram and a blood sample drawn in the fasted state to assess lipid profile (Day 0). Exclusion criteria were: participation in another study during the last 6 month, abnormal ECG, cholesterolemia >5 mmol/l, triglyceridemia >3 mmol/l, pregnancy, history of intestinal intolerance to any type of food, being overweight with BMI >29 kg/m^2, fish consumption more than 3 times weekly or current n-3 PUFA supplementation, and allergy to fish, eggs or soya. The subjects were then instructed to limit their n-3 nutritional intakes from vegetal and fish sources during the study.

2.2. Study design

Study design was a prospective single center open label pharmacokinetic study, and was performed over a 15 days period (Fig. 1), lasting from day 0 until day 15 (D15). Each subject received an 0.6 g/kg n-3 PUFA infusion over 3 h on Day 1 (D01), and ingested an oral 0.2 g/kg n-3 PUFA dose on Days 8, 9 and 10. On both occasions fatty acid membrane composition of platelets and red blood cells (RBC), and blood lipids were monitored during the following 6 days post IV, 5 days post oral. An exercise test was performed at the end of each n-3 PUFA administration (Days 1 and 11).

2.3. N-3 PUFA supplements

The lipid emulsion (10% Omegaven®, Fresenius Kabi AG, Stans, Switzerland) contained 20.1% EPA and 18.4% DHA as well as 0.02 g DL-α-tocopherol per 100 ml. A dose of 0.6 g/kg (i.e. 6 ml/kg) was infused over 3 h: the solution further contains. As this dose exceeded the manufacturer's recommendation, safety variables were included with determination of blood non esterified fatty acids (NEFA), triglyceride and α-tocopherol concentrations. The oral supplementation was delivered over 3 consecutive daily doses of 0.2g n-3 PUFA/kg provided as capsules (Omega 3 Gisand, Bern, Switzerland) containing 1200 mg of fish oil including 453 mf n-3 PUFA as 120 mg EPA + 333 mg DHA. The number of capsules (Table 1) required to match the IV dose was elevated, being the reason why the total dose could not be swallowed on one single day.

2.4. Experimental protocol

The subjects came to the ICU's research facilities of the Lausanne University Hospital on Monday (Day 1) after an overnight fast. A peripheral venous catheter was inserted in each forearm, one for the n-3 PUFA infusion, the other for venous blood sampling. Subjects were monitored with continuous pulse oximetry and non invasive blood pressure was measured every 10 min (Agilent Philips M3 M3046A Patient Monitor, Santa Ana, CA USA). Blood samples were collected at time 0 (i.e. just before starting the infusion),

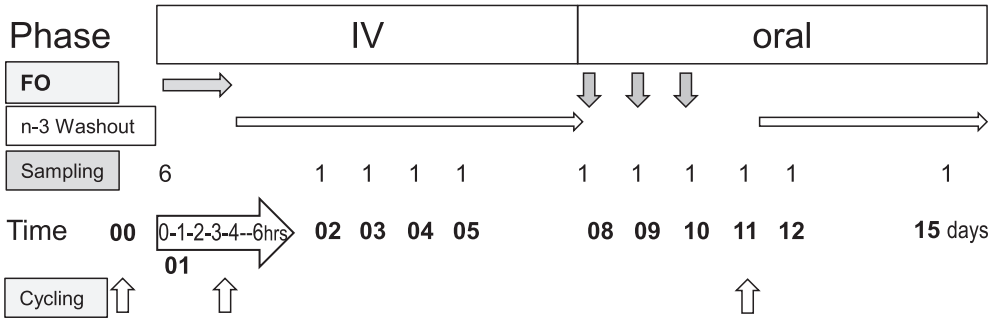

Fig. 1. Study design showing the consecutive and oral sequences.