ORAL COMMUNICATIONS / INCORPORATIONS

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1.

EVALUACIÓN DE SEGURIDAD Y FARMACOCINÉTICA DE UNA NUEVA TERAPIA ANTIOXIDANTE COMBINADA PARA LA LESIÓN POR ISQUEMIA-REPERFUSIÓN MIOCÁRDICA: PERSPECTIVAS DE UN ENSAYO CLÍNICO DE FASE I. Assessing safety and pharmacokinetics of a novel combined antioxidant therapy for myocardial reperfusion injury: phase I clinical trial insights.

Introduction: Treatment of acute myocardial infarction (AMI) with percutaneous coronary intervention (PCI) contributes to until 50% of the infarct size. In this process, termed myocardial reperfusion injury (MRI), oxidative stress plays a pivotal role, and antioxidants are a potential treatment against MRI. We aimed to assess in humans the safety and pharmacokinetics of a combined antioxidant therapy (CAT), composed of ascorbic acid (AA), N-acetylcysteine (NAC), and deferoxamine (DFO). Methods: Placebo-controlled, double-blind phase I clinical trial. 18 healthy subjects were randomized 2:1 to CAT or placebo (NaCl 0.9%) at different intravenous infusion rates (CAT1 and CAT2) for 90 minutes. Blood samples were collected at fixed time intervals to measure the concentration of CAT components (AA, NAC, and DFO). Adverse events (AE) were monitored along and up to 30 days after the infusion. Pharmacokinetics parameters were estimated with a noncompartmental model using R Software. Mixed effects linear regressions were performed to compare drug concentrations over time. Results: Concentrations of all three drugs increased significantly in CAT1 and CAT2, peaking around 30-60 minutes. Mean maximum concentrations (µmol/L) for AA, NAC, and DFO in CAT1 were 704.8, 459.2 and 3.838; in CAT2, 496.7, 573.9, and 3.031. A half-life of 0.945 ± 0.174 hours was estimated for AA, 1.506 ± 0.678 hours for NAC, and 0.545 ± 0.398 hours for DFO. The AUC from 0 to 180 minutes was 1.232 ± 0.386 (mM h), 1.048 ± 0.468 (mM h), and 5.762 ± 2.425 (nM h) for AA, NAC, and DFO. No serious AE were reported. Conclusions: CAT is safe, and plasma drug concentrations potentially useful to counteract oxidative stress in MRI, indicating suitability for a phase II trial in AMI.

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2.

LDL OXIDADA PROMUEVE LA RESISTENCIA FARMACOLÓGICA A LAS TERAPIAS DE NUEVA GENERACIÓN EN CÉLULAS DE CPRC. Oxidized LDL promotes drug resistance to new-generation therapies in CRPC cells.

Advanced prostate cancer (PCa) is dependent on androgens for its proliferation and survival and is therefore treated with androgen deprivation therapy (ADT). Most patients show resistance to treatment and develop castration-resistant PCa (CRPC). CRPC, paradoxically, still depends on androgen receptor (AR) signaling. Two of the mechanisms that explain this phenomenon are: 1) overexpression of AR and constitutively active isoforms such as AR-V7 and 2) intracrine steroidogenesis where the expression of the entire molecular machinery for androgen synthesis is generated from cholesterol for AR activation under ADT conditions. Evidence shows that CRPC cells decrease internal cholesterol synthesis and increase uptake of modified lipoproteins, whereby exogenous cholesterol uptake from the extracellular becomes relevant in CRPC. Here we show that oxidized low-density lipoproteins (oxLDL, a modified form of LDL) and not native low-density lipoproteins (nLDL) contribute significantly to the development of the CRPC phenotype and resistance to new generation therapies such as abiraterone and enzalutamide, by promoting the expression of steroidogenic enzymes and markers of progression in CRPC cells in vitro.

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3.

LDL LA AUTODIFERENCIACIÓN ES UN DESAFÍO EN LA DETERMINACIÓN DE LA SENESCENCIA DE FIBROBLASTOS CARDÍACOS DE RATA ADULTA. The self-differentiation is a challenge in the determination of adult rat cardiac fibroblast senescence.

Aging and cellular senescence emerged as important causes in the progression of cardiovascular diseases. In the heart, cardiac fibroblasts (CF) are sentinel cells that regulate and maintain the architecture in cardiac tissue; consequently, to understanding CF senescence is an important topic to study. The activation of TLR-4 by LPS has been shown to induce cell senescence. However, this cellular type undergoes progressive self-differentiation in 2D culture plates, which is a major challenge in our experimental design. The use of SB-431542, an ALK-5 inhibitor, has been proposed as a strategy to prevent self-differentiation in CF; therefore, we studied if LPS exhibits improved senescence response in adult rat CF cultured in the presence of SB-431542. Objective: Evaluate the role of self-differentiation in the determination of CF senescence triggered by LPS. Methodology: Isolated adult rats CF were cultivated in the presence/absence of SB-431542 until 80% confluency. Subsequently, CFs were treated with LPS for 24 and 72 hours to evaluate the grade of cell differentiation through measurement of α-SMA by immunofluorescence, while markers of cellular senescence were evaluated at 72 hours, including, cell size, SA-β-galactosidase activity, and cell cycle progression protein levels (p16, p53) by western blot. Results: The inhibition of self-differentiation reduces the α-SMA assembly in CF. The treatment of CF with LPS exhibited a greater difference in an SA-β-galactosidase positive CF as well as an increase in cell size as well as p16 and p53 protein levels. Conclusions: The inhibition of self-differentiation improves the LPS performance in the induction of CF senescence.

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4.

INCORPORACIÓN / INCORPORATIONS

ASOCIACIÓN ENTRE POLIMORFISMOS GENÉTICOS INVOLUCRADOS EN LA FARMACOCINÉTICA Y FARMACODINAMIA DE LOS FÁRMACOS OPIOIDES Y LA RESPUESTA AL DOLOR EN PACIENTES CON CÁNCER DE COLON. Association between genetic polymorphisms involved in the pharmacokinetics and pharmacodynamics of opioid drugs and the response to pain in patients with colorectal cancer.

Pain is a common and debilitating symptom in patients with advanced colorectal cancer (CRC), affecting over 70% of patients. Opioids are the first-line treatment for moderate to severe cancer pain, but finding the right dose for each patient can be challenging. Genetic polymorphisms of the COMT gene could help to predict individual variability in the pharmacological response to opioid pain management. The objective of this study was to determine the association between the rs4680 genetic polymorphism of the COMT enzyme and the effectiveness and toxicity of opioids in patients with advanced CRC. This was a multicenter cross-sectional observational study of adult patients with advanced CRC. The genetic profile of tissue samples was analyzed using TaqMan probes. Statistical analysis was performed using measures of dispersion, position and central tendency using the RStudio® software. A total of 37 patients with advanced colorectal cancer were included in the study. The average age of the patients was 72.3 years, and 51% were women. The most commonly used opioid drugs were tramadol, morphine, and fentanyl. 41% of the patients had a G/G, 35% A/G, and 24% A/A genotype. 47.6% of the 21 hospital admissions for pain management were in patients with a G/G genotype. Four of the five patients who required at least one opioid rotation had a G/G genotype, and 41.7% of the twelve patients who had at least one adverse drug reaction to opioids also had a G/G genotype. Patients with advanced colorectal cancer with a G/G genotype for COMT enzyme had an increased risk of experiencing problems with effectiveness and toxicity with the use of opioid drugs.

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