P204  

**N-Acetylcysteine inhibits peroxynitrite-mediated damage in oleic acid-induced lung injury**

O Koksel, I Cinel, L Tamer, L Cinel, A Ozdulger, U Oral  
Mersin University, Turkey


Since oleic acid (OA) induces morphologic and cellular changes similar to those observed in human acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), it has become a widely used model to investigate the effects of several agents on pathogenesis of lung injury. The antioxidant, anti-inflammatory and antiapoptotic properties of N-acetylcysteine (NAC) have been documented in many lung injury models [1]. In this study, we evaluated the role of NAC in an OA-induced lung injury model by measuring myeloperoxidase (MPO) activity, malondialdehyde (MDA) and 3-nitrotyrosine (3-NT) levels in lung tissue.

Five groups (sham, NAC, OA, pre-OA-NAC and post-OA-NAC) were determined. ALI/ARDS was induced by intravenous (IV) administration of OA. The pre-OA-NAC group received IV NAC 15 min before OA infusion and the post-OA-NAC group received IV NAC 2 hours after OA infusion. In both of the NAC treatment groups, blood and tissue samples were collected 4 hours after OA infusion, independent of the time of NAC infusion.

The MPO activity, MDA and 3-NT levels in lung homogenates were found to be increased in the OA group, and the administration of NAC significantly reduced tissue MPO, MDA and 3-NT levels ($P=0.0001$). Lung histopathology was also protected by NAC in this OA-induced experimental lung injury model.

In conclusion, the present study demonstrates that oleic acid induces myeloperoxidase activation and consequently increases 3-NT and MDA levels in lung tissue. Our data suggest that elevated 3-NT levels in lung tissue represent the role of excessive formation of peroxynitrite and the efficacy of NAC treatment in the prevention of peroxynitrite-mediated OA-induced lung injury. Due to its antioxidant and antiinflammatory properties, NAC seems to be a promising agent in treatment of critically ill patients with lung injury states.

Reference

P205  

**Therapeutic neutralization of interferon-gamma in primates prevents lethality in Gram-negative bacteremic shock**

P Lainée1, P Efron2, K Lorré3, L Moldawer2  
1CIT, Evreux, France; 2University of Florida College of Medicine, Gainesville, Florida, USA; 3Innogenetics, Gent, Belgium


**Background**  
The treatment of severe sepsis and septic shock with anticytokine therapies remains a dilemma. Although a number of preclinical studies have shown efficacy in primate models of bacteremic shock when administered prophylactically, these same therapies have a much diminished effectiveness when administered therapeutically.

**Aim**  
This study investigated whether therapeutic administration of a novel antihuman interferon-gamma (anti-IFNγ) monoclonal antibody (mAb) could improve outcome in a lethal model of Gram-negative bacteremic shock.

**Methods**  
Gram-negative bacteremic shock was induced in 14 anesthetized Cynomolgus monkeys by intravenous injection of approximately 10 (10) cfu live Escherichia coli. Treatment was administered only after the animals developed symptoms of shock meeting at least two of the predefined criteria: 30% reduction in blood pressure, 30% increase in heart rate and oliguria (urine output <1 ml/kg body weight/hour). Six of the animals received placebo while eight were treated with 10 mg/kg humanized anti-IFNγ mAb. Invasive hemodynamic monitoring under anesthesia was continued for 12 hours, after which the animals were returned to their cages, and were followed for daily clinical signs during 14 days.

**Results**  
Five out of the six placebo-treated Cynomolgus monkeys died or required euthanasia within 24–72 hours after E. coli challenge, while one animal survived for 5 days. In contrast, six of the eight animals treated with the humanized anti-IFNγ mAb survived for 7–14 days ($P=0.013$ vs placebo). More specifically within the treated group, two animals died early of sepsis (day 3 and day 4, respectively), two animals were euthanized on day 7 because of limb necrosis (caused by catheter-related thrombosis) and not directly because of the sepsis symptoms, one animal was euthanized on day 9 due to sepsis symptoms, and three animals survived 14 days and appeared to be in good health. Treatment with the anti-IFNγ mAb decreased the systemic TNF-α, IL-6 and IL-1β response to E. coli. Furthermore, renal dysfunction, evidenced by increased creatinine, was significantly decreased by treatment with the anti-IFNγ mAb.

**Conclusions**  
This study demonstrates that, in a primate model of E. coli-induced septic shock, the neutralization of IFNγ with a mAb, administered after the onset of clinical signs of sepsis, improves survival and attenuates the pathological changes associated with the development of multiple organ dysfunction. This suggests that IFNγ blockade potentially represents an effective mode of intervention in lethal septic shock.

P206  

**Predicting the response to therapy from a mathematical model**

G Clermont1, R Kumar2, J Bartels3, Y Vodovotz2, S Chang3, C Chow2  
1UPMC, Pittsburgh, Pennsylvania, USA; 2University of Pittsburgh, Pennsylvania, USA; 3Immunetics, Inc., Pittsburgh, Pennsylvania, USA


**Objectives**  
To determine the feasibility and usefulness of computer simulations in evaluating therapeutic strategies and patient selection in clinical trials of sepsis.

**Methods**  
We simulated an interventional trial of a neutralizing body against tissue necrosis factor (anti-TNF) in sepsis based on a mechanistic mathematical model that includes a bacterial infection,