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Protective effect of dexmedetomidine in a rat model of α-naphthylthiourea–induced acute lung injury☆

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ABSTRACT

Background: We assessed the effects of dexmedetomidine in a rat model of α-naphthylthiourea (ANTU)–induced acute lung injury.

Methods: Forty Wistar Albino male rats weighing 200–240 g were divided into 5 groups ($n = 8$ each), including a control group. Thus, there were one ANTU group and three dexmedetomidine groups (10-, 50-, and 100-μg/kg treatment groups), plus a control group. The control group provided the normal base values. The rats in the ANTU group were given 10 mg/kg of ANTU intraperitoneally and the three treatment groups received 10, 50, or 100 μg/kg of dexmedetomidine intraperitoneally 30 min before ANTU application. The rat body weight (BW), pleural effusion (PE), and lung weight (LW) of each group were measured 4 h after ANTU administration. The histopathologic changes were evaluated using hematoxylin-eosin staining.

Results: The mean PE, LW, LW/BW, and PE/BW measurements in the ANTU group were significantly greater than in the control groups and all dexmedetomidine treatment groups ($P < 0.05$). There were also significant decreases in the mean PE, LW, LW/BW and PE/BW values in the dexmedetomidine 50-μg/kg group compared with those in the ANTU group ($P < 0.01$). The inflammation, hemorrhage, and edema scores in the ANTU group were significantly greater than those in the control or dexmedetomidine 50-μg/kg group ($P < 0.01$).

Conclusion: Dexmedetomidine treatment has demonstrated a potential benefit by preventing ANTU-induced acute lung injury in an experimental rat model. Dexmedetomidine could have a potential protective effect on acute lung injury in intensive care patients.

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1. Introduction

Lung protective ventilation strategies have led to a decrease in the mortality rate of acute respiratory distress syndrome (ARDS) patients. However, pharmacologic interventions have revealed little benefit in those patients, with the mortality rate remaining as high as 40%–50% [1–3]. An increase in capillary permeability and the resultant pulmonary edema play a crucial role in the development of ARDS [4]. Pulmonary inflammation and protein-rich alveolar edema leads to acute respiratory failure in these patients [1–4].

Dexmedetomidine is a selective α_2-adrenergic agonist used for sedation and analgesia in critically ill patients. The anti-inflammatory effects of dexmedetomidine have been demonstrated in previous experimental animal models [5–12]. However, although a reduction in pulmonary inflammatory mediators has been shown [6], the absolute result of such a reduction (decreased pulmonary edema) was not demonstrated, which could be important for the clinical implications of the data. If dexmedetomidine has a preventive effect on pulmonary edema development, this effect could be useful in the prevention of ARDS.

Acute lung injury (ALI) is a clinical condition that is the result of a predisposing medical or surgical illness, such as blunt chest trauma, chemical/inhalational injury to the lungs, and septicemia [1–4]. Thus, ALI occurs after previous damage to the chest/body. Most of these clinical scenarios are critical diseases that already necessitate mechanical ventilation in the intensive care unit (ICU) [6]. Dexmedetomidine is used for the sedation of these patients in the ICU [5,6,8,9]. Some of these patients develop ALI later in the course of their primary disease [6]. Therefore, we investigated the inhibitory effects of dexmedetomidine using an experimental pulmonary edema model. α-Naphthylthiourea (ANTU) is a chemical that produces pulmonary edema mediated by an inflammatory response [13–21]. Therefore, we administered dexmedetomidine before the induction of lung injury with ANTU to mimic the clinical scenario that "dexmedetomidine usage in the ICU may prevent the development of ALI."

We hypothesized that dexmedetomidine could attenuate pulmonary edema and pleural effusion. As a sign of pulmonary edema, the primary outcome of our study was determined as the lung weight/body weight (LW/BW) ratio. The secondary outcome measure was pleural effusion (PE).

2. Materials and methods

After obtaining ethical consent from the Animal Research Ethics Committee of Zonguldak Karaelmas University, 40 male adult Wistar albino rats, weighing 200–240 g, were included in the study. The animal study was performed at the Experimental Surgery, Research, and Animal Laboratory of Karaelmas University of Medicine, Faculty of Zonguldak. All rats were kept under standard laboratory conditions with 12-h light/12-h dark cycles and allowed free access to food and water. During the experimental procedure, the rats were placed in separate cages and kept at room temperature (22°C). The procedures and protocols of the study were in accordance with our institutional guidelines, which parallels the Guide for the Care and Use of Laboratory Animals (U.S. National Institutes of Health, revised 1985).

2.1. Experimental protocol

We used an experimental model that had been previously accepted and documented [14–16,20,21]. Before the experimental procedure, all the rats were weighed with an analytical balance, and their body weight (BW) was recorded.

The rats were divided into five equal groups ($n = 8$ each), as follows:

Control group ($n = 8$): Received 2.5 mL/kg olive oil (Sigma, St. Louis, MO) intraperitoneally (ip).

Group ANTU ($n = 8$): Received 10 mg/kg of ANTU (Interchim, Montlucon, France) suspended in olive oil, 4 mg/mL ip.

Dex10 group ($n = 8$): Received 10 μg/kg ip of dexmedetomidine (100 μg/mL; Precedex, Hospira, Lake Forest, IL) and 30 min later received 10 mg/kg of ANTU ip.

Dex50 group ($n = 8$): Received 50 μg/kg ip of dexmedetomidine and 30 min later received 10 mg/kg of ANTU ip.

Dex100 group ($n = 8$): Received 100 μg/kg ip of dexmedetomidine and 30 min later received 10 mg/kg of ANTU ip.

Four hours later, all the rats were anesthetized with thiopental sodium (50 mg/kg ip) and were bled by cutting the abdominal aorta to eliminate blood contamination in the thoracic cavity [14–16,20,21]. Next, the thorax was opened, any pleural effusion was carefully collected with a 1-mL insulin syringe, and the total pleural effusion volume was determined using this syringe, which has measurement marks every 0.1 mL. Care was also taken to eliminate blood contamination in the pleural effusion. All surrounding tissues (including the heart, vascular and lymphatic structures, thymus, and adipossues) were dissected, and the lungs were removed and weighed (LW) with an electronic scale. The volume of PE (in milliliters) and the LW/BW and PE/BW ratios were calculated and considered as an index of pulmonary edema [6–8,14,15].

2.2. Histologic examination

For the histopathologic examination, the lung tissue samples were fixed in 10% formalin immediately after removal, dehydrated in graded concentrations of ethanol, cleared in xylene, and embedded in paraffin. All lung lobes were used for the histologic examination. At least eight tissue sections, 10-μm thick, were obtained and then stained with hematoxylin-eosin. A pathologist performed a blind examination of the sections under a light microscope. All histopathologic changes were documented in each lung tissue sample, including intra-alveolar hemorrhage, alveolar edema, and inflammation. Alveolar edema (swelling of the alveolar wall) and intra-alveolar hemorrhage were scored on a scale from 0 to 3, where 0 = absence of pathology (<5% of maximum pathology), 1 = mild (<10%), 2 = moderate (15%–20%), and 3 = severe (20%–25%) [22,23]. Leukocyte infiltration was evaluated to determinate the severity of alveolar inflammation. Each section was divided into 10 subsections, and leukocyte infiltration was examined in each of the subsections at a magnification of 400× with the following scale: 0 = no extravascular