EFFECT OF DEXAMETHASONE ON THE TREATMENT OF LUNG OEDEMA INDUCED BY OLEIC ACID IN DOGS

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Abstract

The therapeutic effect of 1 mg/kg of dexamethasone on lung oedema and respiratory distress induced by 0.08 mg/kg of oleic acid (OA) in dogs was investigated into 8 dogs. One hour after OA injection, blood pH, HCO3\(^-\), pO2, O2Hb, and heart rate decreased, whereas COHb, pCO2, temperature, and respiration rate increased. Lung oedema was confirmed histopathologically in a dog from the control group who died. Blood pH, COHb, temperature, and respiration rate returned to normal values after administration of dexamethasone. It has been determined that respiratory distress and lung oedema cause important changes in blood gases and the administration of a single dose of 1 mg/kg of dexamethasone is effective in the treatment of lung oedema and respiratory distress induced in dogs by OA.

Key words: dog, lung oedema, oleic acid, dexamethasone.

Lung oedema, respiratory distress, and fat embolism are common disorders and may lead to death (6, 12). The mortality rate of respiratory distress and lung oedema was reported to be as high as 50% and factors contributing to that high occurrence remain to be elucidated (5). Acute respiratory distress syndrome is the prerequisite of acute lung inflammation, characterised by alveolar leukocyte infiltration and pulmonary oedema resulting from acute respiratory failure. Oleic acid (OA) administration is a well-established model to induce diffuse lung disorders, including acute permeability pulmonary oedema, fat embolism, and respiratory distress in canines (4, 8-11, 13).

Lung oedema may occur as a complication of lung diseases, renal dysfunction, and excessive fluid administration in dogs with and without dehydration. In spite of the scientific and technological progress in critical care medicine, there is no specific respiratory distress and lung oedema therapy available. Thus, replacement therapy is applied (6). Corticosteroids may be effective for the treatment of respiratory distress and lung oedema because of their anti-inflammatory effects. Moreover, corticosteroids may limit the cellular toxicity and intercellular oedema formation by decreasing the cellular permeability (1). Dexamethasone was also found to have a beneficial effect in patients with bronchiolitis (14). Bradley et al. (2) investigated the effect of 0.2-0.4 mg/kg continuously applying doses of dexamethasone to lung oedema induced by OA administration and reported that these doses reduced the mortality rate. Therefore, evidence suggests that a single injection of 1 mg/kg of dexamethasone could reduce the concentrations of inflammatory mediators in the lung, inhibit the oedema formation, and repair instability of blood gases, which is regulated by the respiration.

The objectives of this experiment were to examine the therapeutic effect of single bolus injection of dexamethasone in dogs with lung oedema induced by OA and to evaluate the changes of blood gases as well as clinical findings.

Material and Methods

The Ethic Committee of Animal Care and Use in the faculty of Veterinary Medicine in the Ankara University approved this experimental protocol (Decision No. 2004/45). Eight stray dogs at an age of 3.0 ± 1.7 years and weighing average of 11.1 ± 4.9 kg were used to develop lung oedema and respiratory distress by injecting into the jugular vein 0.08 mg/kg of oleic acid (OA) (Merck, USA). After the administration of OA in a prone position, the dogs were kept in this position for at least ten minutes. One hour after OA
injections, the dogs were randomly assigned to receive intravenously into the jugular vein a single bolus injection of 1 mg/kg of dexamethasone (dexa group, n=4) and equivalent volume of physiologic saline solution (control group, n=4). The experimental design and sample collection scheme were summarised in Fig. 1. The baseline showed the initiation of the experiment and the time-point of OA infusion. The black circled point indicated that oleic acid induced lung oedema and respiratory distress. Arterial blood samples and physiological parameters were obtained at each circled time-point during 36 h.

In order to obtain arterial blood, a catheter was placed into the femoral artery and sutured to the skin. Blood samples were collected from the femoral artery just before the injection of OA, 1 h after the injection of OA (just before administration of dexamethasone), 1 h after administration of dexamethasone, and sampling was then continued every 12 h for up to 36 h after the injection of dexamethasone. The dogs breathed spontaneously. Blood samples were put into heparinised vacutainers and then analysed for blood pH, HCO₃⁻, (mmol/L), pCO₂ (mmHg), pO₂ (mmHg), O₂Hb (%), and COHb (%) using blood gas analyser (Chiron Diagnostics, BGA 865, USA). Pulsation (per min), rectal temperature, and respiration (per min) were also monitored on the time of blood sampling. Samples from the lung, liver, brain, and kidney of the dog from the control group, who died due to lung oedema at the 36th h

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In data analyses, 2-way ANOVA as repeated measured with time being subplot was used and the linear model included the effects of treatments (dexamethasone and saline), sampling time, and treatment by sampling time interaction. Differences between group means were attained using the Tukey’s post hoc test and declared to be significant at P<0.05 (SPSS, Version 10.0 Chicago, USA).

Results

All the animals were in clinically normal health status before the experiment. After being given a bolus injection of OA, the animals started to breathe shallowly and faster in a couple of minutes. One hour after OA administration, all the animals displayed the signs of acute respiratory distress. In the control group, this condition remained unchanged during all the experiment.

Respiration increased significantly in both groups 1 h after OA injection as compared with the baseline (P<0.001). In the dexa group, it tended to return to its baseline within 1 h and remained at its steady state until the 36th h, whereas in the control group it was significantly higher than that in the dexa group (P=0.004) until the 36th h (Fig. 2). The body temperature in both groups increased slightly 1 h after OA injection. However, the temperature in the dexa group started first to decrease and then remained at its steady state from 12 h to 36 h (P<0.01) (Fig. 3). The heart rate slightly decreased in both groups 1 h after OA injection as compared with the baseline. At the 12th h, the heart rate increased in both groups, but it decreased again in the dexa group versus the control group at the 36th h (P=0.007) (Fig. 4).

Blood pH insignificantly decreased in both groups 1 h after OA injection as compared with the baseline. However, in the dexa group conversely to control group (P<0.01), it started first to decrease and then reached its steady state from 12 h to 36 h after dexamethasone administration. In the control group, at the 36th h, pH increased changing its value in opposite direction of that of dexa group (Fig. 5).

Blood pressure of CO₂ tended to increase 1 h after OA injection in both groups. However, at the 24th h it decreased in the control group versus dexa group, though without statistical significance, and gained its steady state at the 36th h (Fig. 6). Blood pressure of O₂ slightly decreased in both groups 1 h after OA injection as compared with the baseline. It increased significantly (P<0.001) in the dexa group versus the control group at the 2nd h and tended to return to its baseline but remained at a high level from 12 h to 24 h after the treatment (P<0.05) (Fig. 7).

The percentage of O₂Hb insignificantly decreased in both group 1 h after the OA injection as compared with the baseline. Conversely, pO₂ significantly increased in the dexa group as compared with the control group at the 1st h (P<0.05), but returned to its baseline and then became stable. On the other hand, pO₂ increased in the control group from 24 h to 36 h (Fig. 8). The percentage of COHb slightly increased in both groups 1 h after OA injection as compared with the baseline and tended to return to its baseline from 24 h to 36 h and then became stable (Fig. 9). HCO₃⁻ tended to decrease in both groups, but it decreased more in control group versus the dexa group (Fig. 10).

Necropsy was performed on a dog from the control group, whose death was related to lung oedema. The lungs were oedematous and other organs were of a normal appearance. Histopathologically, there were diffuse exudates related to oedema in the alveolar lumens, thickened alveolar septum, hyaline membranes, and the existence of inflammatory cells including leukocyte infiltration in alveolar spaces (Fig. 11). There were no significant alterations in the brain, liver, and kidneys.
Fig. 1. Time-points of arterial blood sampling to determine physiological parameters in the dexta and control groups.

Fig. 2. Respiration in both groups. Bars represent standard deviation.

Fig. 3. Temperature in both groups. Bars represent standard deviation.
Fig. 4. Heart rate in both groups. Bars represent standard deviation. Bpm represents beats per min.

Fig. 5. The value of pH in both groups. Bars represent standard deviation.

Fig. 6. Pressure of carbon dioxide in both groups. Bars represent standard deviation.
Fig. 7. Pressure of oxygen in both groups. Bars represent standard deviation.

Fig. 8. Oxyhaemoglobin in both groups. Bars represent standard deviation.

Fig. 9. Carboxyhaemoglobin in both groups. Bars represent standard deviation.
Discussion

Immediately after intravenous administration into the jugular vein, OA directly reaches the right atrium and ventricle, and finally it reaches the lungs via the pulmonary artery. Therefore, fat embolism and lung oedema occur in the lung concurrently (7). Bradley et al. (2) proved that OA induces intra-alveolar and interstitial oedema in dogs between the 7th and 72nd h after its administration. Lung oedema was confirmed histopathologically in the dog from control group, who died during the experiment (Fig.11). Furthermore, lung oedema and respiratory distress were confirmed by the changes in blood gases and clinical symptoms. Blood pH, PO₂, and HCO₃⁻, and the percentage of O₂Hb decreased while the percentage of COHb and respiration increased in both groups 1 h after the OA injection as compared to the baseline, indicating an occurrence of lung oedema. Rapid and shallow respiration was also detected in both groups 1 h after the OA injection.

The respiration in the dexamethasone group tended to return to its baseline at the 1st h, and became stable at the 36th h, which indicated the efficacy of dexamethasone. Conversely, respiration in the control group remained higher than that in the dexamethasone group (P=0.004) at the 36th h. An increase in CO₂ 1 h after the dexamethasone injection was higher in the dexamethasone group than in the control group and tended to return to its baseline. In the control group, respiration increased while PCO₂ and H⁺ concentration decreased, which resulted in an increase of blood pH at the 36th h. H⁺ and HCO₃⁻ are coupled in the presence of carbonic anhydrase. The following formula (3) summarises the ion changes during increased respiration that influence pH.

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\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2
\]

In a study designed by Bradley et al. (2), blood pH and PO₂ decreased, whereas PCO₂ increased after...
0.15 ml/kg of OA injected intravenously. Molloy et al. (7) ascertained lung oedema induced by 0.08 ml/kg of the intravenous injection of OA, emphasizing that the oleic acid pulmonary oedema mimics the clinical adult respiratory distress syndrome.

In the present study, a decrease in blood PO$_2$, 1 h after the OA injection is in agreement with the findings of Su et al. (10). Dexamethasone significantly increased PO$_2$, suggesting the use of corticosteroid in lung oedema and respiratory distress. Su et al. (10) noted that the mechanical ventilation improves the oxygenation in the blood in dogs with lung oedema induced by OA. Molloy et al. (7) investigated the therapeutic effects of dopatmine, furosemide, and hydralazine on lung oedema induced by OA in dogs. In dogs given hydralazine, cardiac output and systemic vascular resistance remained constant, whereas in dopatmine and furosemide groups decreased. However, PO$_2$ decreased in all groups including the control groups.

The data clearly shows that COHb increased, while O$_2$Hb decreased 1 h after OA injection, indicating respiratory distress. COHb tended to decrease in control group at the 12$^{th}$ to 36$^{th}$ h, while it remained high in the dexa group. The expectation was that COHb should decrease and O$_2$Hb should increase in the dexa group with the anticipation of the beneficial effect of the treatment. These changes are strongly linked to respiration. Thus, COHb decreased and O$_2$Hb increased versus time in the control group because of increased respiration.

The body temperature was consistent with the respiration in both groups. When the body temperature increased, the respiration increased consistently in the control group. However, in the dexa group the body temperature decreased while the respiration decreased. The heart rate was also consistent with the respiration.

Following lung oedema induction by OA, Bradley et al. (2) administered to dogs dexamethasone, starting 10 min after OA injection. The 0.4 mg/kg dose was given for up to the 36$^{th}$ h and the treatment was then continued for up to the 60$^{th}$ h with 0.2 mg/kg dosage. Three out of 10 dogs in the treatment group died. In this study, the dose of 1 mg/kg of dexamethasone was effective in treatment of lung oedema and respiratory distress induced by OA, even though dexamethasone was given 1 h after OA injection.

In conclusion, blood gas analysis and clinical observations confirmed the presence of lung oedema and respiratory distress after administration of OA. One hour after injection of OA, blood pH, HCO$_3^-$, pO$_2$, O$_2$Hb, and the heart rate decreased while COHb, pCO$_2$, temperature, and respiration increased in all animals. After injection of dexamethasone, 1 mg/kg, blood pH, COHb, temperature, and respiration decreased to normal ranges, conversely to the control group. HCO$_3^-$ remained stable but it was higher than that in the control group. On the other hand, pO$_2$ and pCO$_2$ increased in the dexa group versus control. It was found that the respiration plays a significant role in altering gas exchange. OA injection induces the lung oedema and respiratory distress and a single injection of dexamethasone is effective in the treatment of the disorders.

References