The effect of low molecular weight dextran on haemodynamics and respiratory function during endotoxin-induced shock

J. T. CHRISTENSON, A. AL-SARRAF & R. ABU-SALEH

Department of Surgery, Faculty of Medicine, Kuwait University, Kuwait

SUMMARY

The effects of low molecular weight dextran (LMWD) infusion, on gas exchange and haemodynamics were evaluated in sheep during endotoxin shock. The infusion of LMWD was started after signs of shock and lung injury were evident. After a stabilization period 10 μg kg⁻¹ E. Coli endotoxin was infused i.v.. Endotoxin infusion resulted in an marked increase in pulmonary artery pressure (PAP) and decrease in mean arterial pressure (MAP), respiratory compliance, arterial oxygen tension (PₐO₂) and oxygen delivery index (Do₂I). After 3 h MAP, PₐO₂, Do₂I and compliance improved significantly in LMWD treated animals. The PAP had also decreased significantly in the LMWD-treated animals, but remained high in the controls (P < 0.01).

It was concluded that LMWD infusion improves haemodynamics and gas-exchange in sheep during endotoxin shock.

INTRODUCTION

Lung injury caused by E. Coli endotoxin is characterized by pulmonary hypertension and increased microvascular permeability, resulting in decreased lung compliance and worsened gas exchange (Kux et al., 1972; Brigham, 1986; Modig, 1986; Weigelt et al., 1987). Despite great efforts and improved facilities, mortality from adult respiratory distress syndrome, ARDS, still remains high (Pontoppiden, 1985).

Both in vitro and in vivo studies have shown that pulmonary sequestration of
platelets occurs after endotoxin induced shock (Myrvold & Lewis, 1977, Christenson et al., 1987). Furthermore, it has been suggested that such platelet accumulation in the lungs leads to the release of vasoactive substances (Brigham, 1985), sequestration, margination and disruption of leucocytes in the pulmonary capillaries (Coalsson et al., 1970, Christenson et al., 1987) and decreased amount of surfactant (Harrison et al., 1969).

Low molecular weight dextran, LMWD, (MW 40,000) has a marked effect on the blood flow to various organs, mainly due to a high degree of haemodilution and the concomitant marked decrease in blood viscosity (Lindberg & Darle, 1977). Furthermore, it has been demonstrated previously that LMWD also has a direct effect on the platelets by inhibiting aggregation and increases the deformability of the red blood cells, thus improving blood flow in the microcirculation (Christenson et al., 1987). From experimental studies it has been established that the permeability of the pulmonary alveolar capillary membrane is increased during endotoxaemia for substances up to 10400 MW (Fischer et al., 1977). LMWD should therefore be a suitable substance for improving the microcirculation, without risk of escaping from the vascular compartment.

The objective of the present communication was to evaluate the effects of LMWD on haemodynamics and gas-exchange when administrated after endotoxic challenge, when signs of endotoxic shock had already developed, thus mimicking more closely the clinical situation.

MATERIAL & METHODS

Animal preparation

Eighteen apparently healthy, fasting, adult Australian sheep, weighing 35–40 kg, were anaesthetized with sodium thiopentone (Intraval R., May & Baker Ltd, London, U.K.), 25 mg kg⁻¹ body wt intravenously. Oral intubation and anaesthesia were thereafter maintained with a continuous i.v. infusion of ketamine (Ketalar R., Parke Davis Ltd, London, U.K.), 2 mg kg⁻¹ h⁻¹ and pancuronium, 0.05 mg kg⁻¹ h⁻¹. The animals were ventilated with a mixture of air and oxygen (Fio₂ = 0.5), via an endotracheal tube using positive end-expiratory pressure (Servo 900C, Siemens Elema, Stockholm, Sweden) and PₐCO₂ was maintained between 33 and 45 torr. A large sized nasogastric tube was placed with free drainage in order to evacuate stomach contents and prevent stomach dilatation due to air accumulation. Abdominal aortic, pulmonary artery (7F balloon tipped with thermistor, Edwards Lab. Inc., CA, U.S.A.) and central venous catheters were inserted through groin incisions via femoral artery and veins. After 2 h of stabilization baseline measurements were registered and all animals received E. Coli endotoxin (0127:B8, Difco Lab., Detroit, MI, U.S.A.), 10 μg kg⁻¹ body wt, intravenously infused over a period of 15 min.

Thirty min after the endotoxin challenge (t = 30) nine animals (Group A) were randomly chosen to receive i.v. infusion of LMWD (Dextran-40 in saline, Braun, Meslungen, Düsseldorf, Germany), 15 ml hr⁻¹ kg⁻¹ body wt during 4 h, while the
remaining nine animals (Group B) received only normal saline infused i.v. in the same amount and rate as in Group A and served as controls. Measurements were obtained every half hour after the endotoxin infusion and at t = 240 min the animals were killed. The lungs were removed and weighed before (wet wt) and after drying (dry wt) at 70°C in a laboratory dryer for 7 days. A wet wt/dry wt ratio of lungs were calculated and compared with lungs from untreated normal sheep (n = 10).

**Measured parameters and analysis**

Heart rate (HR, bpm) was measured from the systemic arterial blood pressure curve. Mean arterial blood pressure (MAP, mmHg), central venous pressure (CVP, mmHg), pulmonary artery pressure (PAP, mmHg) and pulmonary capillary wedge pressure (PCWP, mmHg) were recorded with quartz pressure transducers 129A, Hewlett-Packard Andorex, MA, USA) and displayed intermittently on a printer (7754A, Hewlett-Packard, Andorex, MA, USA). Cardiac output (CO, l min⁻¹) was measured by a thermodilution technique (mean value of 3 readings, Cardiac output computer 9250, Edwards Lab. Inc., CA, U.S.A.) and cardiac index (Cl, l m⁻² min⁻¹) was calculated as CO divided by the surface area (SA = body wt x 0.015 + 0.489). Systemic vascular resistance (SVR) was calculated as MAP-CVP/Cl mmHg l⁻¹ m² min⁻¹. Pulmonary vascular resistance (PVR) was calculated as PAP-PCWP/Cl mmHg l⁻¹ m² min⁻¹. Central venous temperature (°C) was recorded from the thermistor in the pulmonary artery catheter. The total respiratory compliance (chest and lung; Cl ml cm⁻¹ water) was calculated as end-inspiratory airway pressure (PaW) divided by tidal volume (TV) both recorded simultaneously from the ventilator. Samples for arterial and venous blood gases were withdrawn simultaneously from the aortic and pulmonary catheters respectively and immediately analysed in a blood gas analyser (Automatic Gas Check, AVL 940, Basle, Switzerland).

Arterial oxygen content (CaO₂) was calculated as 1.3 x Hb x %O₂ saturation/100 x 0.003 x P0₂; (Hb = haemoglobin g dl⁻¹) and oxygen delivery (Do₂) was calculated as Cl x CaO₂.

Venous blood samples were withdrawn every half hour and 1u was added to a red cell haemolysing solution and after dilution, platelets and leucocytes were counted in a haemocytometer using a phase contrast microscope.

**Statistical analysis**

Data from each group were summarized as mean ± standard deviation. The Wilcoxon Rank Sum Test was employed to evaluate changes within a group and to determine differences between groups. P < 0.05 was considered statistically significant.
RESULTS

All animals survived the entire experimental period. No significant differences between the groups, in any of the measured parameters, occurred during the baseline period or 30 min after endotoxin infusion (Fig. 1 & Table 1). Endotoxin infusion resulted in a marked rise in PAP in both groups after 15 and 30 min. In

Fig. 1. Mean arterial pressure (MAP, mmHg), mean pulmonary pressure (PAP, mmHg), cardiac index (Cl, l m⁻² min⁻¹) and respiratory compliance C₁, ml cm⁻¹ H₂O) in 18 sheep given i.v. infusion of endotoxin over 15 min at t = 0. In Group A (●●●; n = 9) LMWD infusion, 15 ml h⁻¹ kg⁻¹ body wt i.v. was started 30 min after endotoxin and continued until the end of the experiment (t = 240). Group B (■■■; n = 9) received no treatment and served as controls. * P < 0.05, *** P < 0.001 for difference between groups. Mean ± SD.
Effect of LMWD during endotoxin-induced shock

Table 1. Arterial oxygen tension ($P_aO_2$) mmHg, Oxygen delivery index (DO$_2$I), systemic vascular resistance (SVR, mmHg l$^{-1}$m$^2$ min$^{-1}$) and pulmonary vascular resistance (PVR, mmHg l$^{-1}$m$^2$ min$^{-1}$) in 18 sheep given i.v. infusion of endotoxin over 15 min (10 µg kg$^{-1}$ body wt, at t = 0). In Group A (n = 9), LMWD infusion, 15 ml h$^{-1}$ kg$^{-1}$ body wt i.v., was started 30 min, after endotoxin and continued until the end of the experiment (t = 240). Group B (n = 9) received no treatment and served as controls. Mean ± SD.

<table>
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<th>Parameter</th>
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<th>30</th>
<th>60</th>
<th>120</th>
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<td>97 ± 13</td>
<td>81 ± 12</td>
<td>84 ± 6</td>
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<td>58 ± 11</td>
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<tr>
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<td>67 ± 4</td>
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<td>102 ± 11</td>
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<tr>
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<td>60 ± 6</td>
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<td>21 ± 0.7</td>
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<td>22 ± 0.8</td>
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<td>19 ± 0.9</td>
<td>8 ± 0.5</td>
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the control group (B) PAP increased slightly towards the end of the study, while in the LMWD-treated animals (Group A) PAP showed a decrease. The static compliance, oxygen delivery index and the $P_aO_2$ showed a decrease. PCWD, Cl and HR remained unchanged in both groups (Fig. 1).

One h after the endotoxin challenge the MAP was decreased to half the baseline values in both groups, but recovered more rapidly in Group A compared to controls (Fig. 1). $P_aO_2$ and compliance showed a sharp drop initially after endotoxin infusion. However, both parameters revealed a partial improvement in group A animals, while they remained at a low level in control (Group B) animals (Table 1 & Fig. 1). The oxygen delivery index also decreased following endotoxin, but returned to baseline values 60 min later in both groups. It remained unchanged in Group A, while in Group B a gradual decrease towards the end of the experiment occurred (Table 1).

The Cl did not change in Group A animals, throughout the experimental period, but increased significantly in Group B followed by a gradual decrease later. After an initial peak at 15 min PVR and PAP dropped in both the groups 45 min later (Fig. 1 & Table 1). Both these parameters showed an increase in Group B during the observation period, but remained basically unchanged in Group A (Fig. 1 & Table 1).

Cell and platelet counts decreased significantly in both groups after the endotoxin challenge and remained low in Group B throughout the experiment, while in Group A a significant increase was observed (Fig. 2).

The wet/dry wt ratio was 5.46 ± 0.4 in Group B, 4.78 ± 0.3 in Group A ($P < 0.05$) compared to normal control lungs, 4.65 ± 0.1.
Fig. 2. Laboratory data for two groups of sheep given endotoxin, group B, a control group (■——■) and group A, treated with LMWD (○——○) 30 min after endotoxin. Platelet count (PLTS, as percentage of baseline value, t = 0) and leucocyte count (WBC, as percentage of baseline value, t = 0).

DISCUSSION

Clinical and septic shock in human, causes characteristic haemodynamic and respiratory changes which are also seen after intravenous infusion of endotoxin in experimental animal models. Pulmonary hypertension and increased vascular permeability are features of experimental endotoxin induced shock (Demling, 1982). Factors which might contribute to the pulmonary response in endotoxic shock include release of vasoactive substances (Kux et al., 1972), mechanical blockage of capillaries by platelet aggregates (Robb et al., 1972; Demling, 1980, Christenson et al., 1989) and degranulated and fragmented leucocyte sequestration in several vascular beds following endotoxin challenge (Coalson et al., 1975; Brigham, 1985; Moon et al., 1986).

Lung injury caused by E. Coli endotoxin is characterized by an early pulmonary
hypertension (the hypertensive phase), where the pulmonary artery pressure is usually more than doubled and accompanied by hypoxia as well as decreased lung compliance. This hypertensive phase is followed, within 1–2 h, by increased pulmonary microvascular permeability, causing non-cardiac pulmonary oedema or respiratory distress syndrome (permeability phase) (Brigham et al., 1979; Sigurdson & Christenson, 1988). In the present communication we have used an experimental protocol designed to mimic the clinical situation. The animals were given fluids in large amounts to prevent hypovolaemic shock, CVP and PCWP were kept constant, to limit possible deleterious effects on splanchnic and renal blood flow. Endotoxin was infused i.v. in a rather moderate dose, 10 μg h⁻¹. The animals were treated with controlled ventilation on a quite high inspired oxygen concentration (50%) to avoid hypercarbia and severe hypoxaemia.

After endotoxin infusion a sharp drop in MAP and PaO₂ and a rise in PAP was observed in both groups. However, after the start of the infusion of LMWD a gradual improvement in PaO₂, oxygen delivery index, lung compliance, MAP and PVR occurred. The exact mechanism of action of LMWD is not yet clear. Two major features of LMWD that have been regarded as most important are (a) haemodilution, which leads to a decreased blood viscosity and thereby improved flow in the microcirculation, and (b) a direct effect on the platelets resulting in decreased platelet adhesiveness (Gruber & Messmer, 1977; Al Huneidi et al., 1988). Dextran is absorbed to the surface of the platelets and thereby alters the negative charge leading to less platelet adhesivity (Gruber & Bergentz, 1966). The increased platelet aggregation during endotoxinaemia, described previously, is thought to lead to their entrapment in the lungs and their release of vasoactive substances, which will subsequently cause an increased pulmonary vascular resistance (Kux et al., 1972, Al Sarraf, 1988). Platelet aggregation also accelerates the formation of a network of fibrin, trapping both red and white blood cells (Cooper et al., 1984).

Leucocyte trapping has been described recently in an in vivo model (Sigurdsson et al., 1989). The role of leucocytes in endotoxin induced shock has been discussed extensively as they are thought to be a major source of oxygen-free radicals. Even though LMWD does not have any direct effects on leucocytes, it is possible that by preventing platelet aggregation and sequestration less fibrin is deposited and fewer leucocytes are trapped, an effect which is enhanced by the haemodilution and lowered blood viscosity. In conclusion low molecular weight dextran (LMWD) significantly improved haemodynamics and gas-exchange during endotoxin-induced shock in a sheep model, despite the fact that LMWD-infusion was started when the first signs of shock and lung injury developed. It appears that the effect of LMWD is due to haemodilution and diminished platelet adhesiveness, secondarily leading to less trapping of leucocytes in the pulmonary microcirculation.

ACKNOWLEDGEMENTS

This study was supported by Grant MS 008, Kuwait University Research Council, Kuwait.
REFERENCES


