Hypoxaemia and suspected pulmonary oedema in a Dorper ewe after diazepam-ketamine induction of anaesthesia

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ABSTRACT

Anaesthesia was required in an 18-month-old Dorper ewe scheduled for surgical repair of an abdominal hernia. Anaesthesia was induced with diazepam (0.15 mg/kg) and ketamine (6 mg/kg), and maintained with halothane in oxygen on a circle anaesthetic machine. Hypotension, hypoxaemia, cyanosis and pulmonary oedema were observed from the start of surgery, but the symptoms improved towards the completion of the procedure. The aetiology of this condition could not be established. It is suggested that propylene glycol, the organic solvent in the diazepam formulation, may have stimulated the release of vasoactive substances that resulted in pulmonary oedema.

Key words: anaesthesia, diazepam, hypoxaemia, ketamine, propylene glycol, pulmonary oedema, sheep.

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Anaesthesia was required in a 67 kg, 18-month-old Dorper ewe for surgical correction of an abdominal hernia. Apart from the surgical problem, the ewe appeared clinically normal after physical and haematological examination. Water and food were withheld for 12 h. Venipuncture was performed in the jugular vein for the induction of anaesthesia and the administration of lactated Ringer solution during surgery. Anaesthesia was induced with a combination of diazepam (Valium, Roche) at 0.15 mg/kg (10 mg total dose) administered over 10 sec and ketamine hydrochloride (Anaket, Centaur Labs) at 6 mg/kg (402 mg total dose). After tracheal intubation, anaesthesia was maintained with halothane (Fluothane, Zeneca) in oxygen on a circle anaesthetic machine. Ventilation was controlled. When suturing of the skin commenced at completion of surgery, the halothane was turned off and the sheep was allowed to breathe spontaneously. For intraoperative monitoring, multi-parameter physiological monitors were used. Arterial blood pressure was measured directly with a calibrated strain gauge transducer from a catheter introduced into the radial artery. The monitored variables were recorded on a standard monitoring sheet. The cardiopulmonary variables before and after diazepam/ketamine administration and during halothane maintenance are summarised in Table 1. The results of the arterial blood-gas analysis during maintenance are summarised in Table 2. Injection of diazepam induced sedation with minimal changes in heart rate and arterial blood pressure. Ketamine administration induced anaesthesia that was associated with a 38 % decrease in mean arterial blood pressure. During surgery, mean arterial blood pressure improved to values similar to the values observed after diazepam administration.

During endotracheal intubation, moist 'gurgling' ventilatory noises were heard, and assumed to be the result of saliva accumulating in the pharynx and larynx. During surgery, respiratory sounds from the endotracheal tube became audible and white froth appeared in the transparent spirometer sensor connected to the endotracheal tube. The froth was suctioned twice from the tube to reduce respiratory obstruction during ventilation. Cyanosis of the mucous membranes was observed, and arterial blood was collected for blood-gas analysis. The ventilatory sounds reduced progressively and disappeared near completion of surgery. Surgery lasted approximately 60 min. The mean tidal volume decreased from 561 (±24) mℓ during controlled ventilation to a mean of 382 (±19) mℓ during spontaneous ventilation at completion of surgery. Although the end-tidal carbon dioxide concentration was maintained within acceptable clinical limits during halothane anaesthesia, the blood-gas analysis indicated respiratory acidosis and therefore inadequate alveolar ventilation in the oedematous lungs at an inspiratory pressure of 25 cm H_2O. After extubation, oxygen was administered with a face mask until the ewe recovered from anaesthesia. Evaluation of the superficial mucous membranes did not reveal cyanosis during recovery. Postoperative recovery was uneventful.

The use of diazepam in combination with ketamine for induction of anaesthesia in sheep has been described[6], but pulmonary oedema has not been reported as an adverse effect. Hypoxaemia and pulmonary oedema were described in sheep after the use of xylazine[3,11]. Transient hypoxaemia has been reported in sheep

Table 1: **Perioperative cardiopulmonary variables after diazepam/ketamine induction and halothane maintenance for abdominal surgery in a Dorper ewe.**

	V_t	$ETCO_2$	Hr	Sys	Dia	Mean
Preind[a]	–	–	157	19.2	16.1	17.1
Diaz[b]	–	–	161	17.6	14.4	15.4
Diaz/ket[c]	–	–	135	14.4	8.6	10.6
Haloth[d]	561 (24)	6.4 (0.4)	114 (18)	16.7 (1.4)	12.7 (1.8)	14 (1.6)

V_t: tidal volume (mℓ); $ETCO_2$: end-tidal carbon dioxide concentration (%); Hr: heart rate (beats/min), Sys: systolic blood pressure (kPa); Dia: diastolic blood pressure (kPa); Mean: mean arterial blood pressure (kPa).
[a]Variables before induction.
[b]Variables after diazepam administration.
[c]Variables after diazepam/ketamine administration.
[d]Mean (±SD) for cardiopulmonary variables during halothane anaesthesia.

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Table 2: **Intra-operative arterial blood-gas variables after diazepam/ketamine induction and halothane maintenance for abdominal surgery in a Dorper ewe.**

Time[a]	pH	PCO_2	PO_2	HCO_3	BE	SAT
30 min	7.3	7.2	7.7	27.7	0.6	87
60 min	7.2	8.7	10.0	30.7	3.5	93

PCO_2: arterial partial pressure of carbon dioxide (kPa).
PO_2: arterial partial pressure of oxygen (kPa).
HCO_3: bicarbonate concentration (mmol/ℓ).
BE: base excess (mmol/ℓ).
SAT: oxyhaemoglobin saturation (%).
[a]Time (min) after commencement of surgery.

after intravenous administration of diazepam[4]. Hypoventilation and hypoxaemia were reported after the use of midazolam or diazepam in goats[10] and sheep[12], respectively. Possible causes of lung oedema are cardiac failure, low plasma oncotic pressure, *e.g.* with hypoproteinaemia, pulmonary hypertension or increased pulmonary capillary permeability. An investigation into the effects of diazepam/ketamine in sheep indicated that pulmonary arterial blood pressure decreased in sheep[4]. Xylazine-induced hypoxaemia and pulmonary oedema in sheep are mediated by the peripheral activation of α_2-adrenergic receptors on pulmonary macrophages, resulting in pulmonary capillary damage[1,2]. The presence of hypoxaemia in the ewe despite the high inspired oxygen concentration may also indicate a high pulmonary shunt fraction during anaesthesia.

Possible adverse reactions to propylene glycol, the solvent in the diazepam formulation, may occur. In man, pain on intravenous injection[8], and histamine release from either osmotic damage to tissue and blood cells or an allergic reaction to the solvent occur. The allergic reaction is associated with tachycardia and hypotension[5]. In calves, the use of formulations containing propylene glycol results in histamine release that is associated with increases in pulmonary arterial pressure, decreases in heart rate, cardiac output and stroke volume[7]. In sheep, propylene glycol results in pulmonary hypertension as result of an increase in pulmonary vascular resistance. Pulmonary intravascular macrophages in the lungs of sheep release thromboxane A_2 after propylene glycol administration[9]. The activation of pulmonary macrophages is possibly the common mechanism responsible for the pulmonary effects seen in sheep. Therefore, the combined effect of the pulmonary release of histamine and/or thromboxane may result in pulmonary hypertension, oedema and hypoxaemia. In this case minimal changes in heart rate and arterial blood pressure occurred after diazepam injection, and decreases were only evident after ketamine administration. Owing to the short interval between diazepam and ketamine administration, the observed hypotension may have resulted from the diazepam and not the ketamine. During halothane anaesthesia, when the presence of pulmonary oedema was obvious, the blood pressure returned to the values observed after diazepam administration.

In conclusion, hypoxaemia and transient pulmonary oedema were observed after rapid intravenous injection of diazepam and ketamine. It is speculated that the intravenous administration of propylene glycol in the Dorper ewe activated the release of vasoactive substances from pulmonary intravascular macrophages. This resulted in pulmonary hypertension and/or an increase in pulmonary capillary permeability, pulmonary oedema, and hypoxaemia.

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