Available online at www.sciencedirect.com
ScienceDirect
The Veterinary Journal 177 (2008) 94–103
The Veterinary Journal
www.elsevier.com/locate/tvjl

# The effects on maternal and fetal cardiovascular and acid–base variables after the administration of etomidate in the pregnant ewe

Laura Fresno *, Anna Andaluz, Xavier Moll, Félix García

*Department of Animal Medicine and Surgery, Veterinary College of the Autonomous University of Barcelona, 08193 Bellaterra (Cerdanyola del Vallès), Barcelona, Spain*

Accepted 28 March 2007

**Abstract**

Etomidate is an intravenous (IV) hypnotic agent characterised by its cardiovascular stability. Although etomidate has been satisfactorily used in veterinary and human obstetrics, little is known about its effects on the fetus. This study determined the cardiovascular and acid–base effects of etomidate administration in the pregnant ewe and her fetus. The effects of etomidate were evaluated in two separate studies. In the first study, etomidate was administered as a 1 mg/kg IV bolus; in the second, the drug was administered as a continuous infusion of 100 μg/kg/min for 1 h, preceded by a 1 mg/kg IV bolus.

Etomidate administration did not depress cardiovascular function in the pregnant ewe or fetus. When administered as a continuous infusion, maternal heart rate and blood pressure increased during the second half of the infusion and the initial stages of recovery. Acid–base alterations led to transient but slight respiratory depression in both mother and fetus, probably reflecting the combined effects of etomidate on respiration and the positioning of the animal.


*Keywords:* Etomidate; Ewe; Fetal; Placental transfer; Effects

## Introduction

The non-barbiturate intravenous (IV) general anaesthetic etomidate is a carboxylated imidazole derivative first introduced into clinical practice in 1973. Etomidate has been used both for anaesthetic induction and anaesthetic maintenance in both human and veterinary anaesthesia (Gooding and Corssen, 1976; Kay, 1976; Oduro et al., 1983; Pablo and Bailey, 1999).

Etomidate has a rapid onset of action and fast recovery (Fragen and Caldwell, 1979). It does not release histamine (Doenicke et al., 1973), does not produce immunosuppression (Doenicke and Kropp, 1976), and its cardiovascular stability compared to other induction agents makes it a useful and safe agent for general anaesthesia (Morgan et al., 1975; Gooding and Corssen, 1977; Criado et al., 1980; Brüssel et al., 1989; Scheffer et al., 1993). No organ toxicity or teratogenicity has been reported (Fragen et al., 1976; Friedman, 1988). Adverse effects associated with etomidate include myoclonus and pain during injection (Holdcroft et al., 1976; Helmers et al., 1981; Muir and Mason, 1989; Doenicke et al., 1999), nausea or vomiting (Fragen and Caldwell, 1979; Muir and Mason, 1989), salivation (Carroll and Hartsfield, 1996), and transient adrenocortical suppression in both mother and neonate (Wagner and White, 1984; Kruse-Elliott et al., 1987; Reddy et al., 1988; Crozier et al., 1993; Moon, 1997).

The properties of etomidate have made it a useful agent for obstetric anaesthesia since 1979 (Downing et al., 1979; Gregory and Davidson, 1991). The drug appears to have little or no influence on the acid–base status of the mother or the infant (Regaert and Noorduin, 1984) and a satisfactory clinical status of the newborn has been reported after caesarean delivery (Downing et al., 1979; Giese and

* Corresponding author. Tel.: +34 93 581 15 12/677 97 47 99; fax: +34 93 581 33 25.
*E-mail address:* laura.fresno@uab.es (L. Fresno).

1090-0233/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tvjl.2007.03.023

Stanley, 1983; Regaert and Noorduin, 1984; Gregory and Davidson, 1991; Esener et al., 1992). Moreover, the offspring of mothers given etomidate for anaesthetic induction were found to have a shorter "time to sustained respiration" than those born to mothers who had received thiopental (Downing et al., 1979).

Although etomidate has been used satisfactorily in obstetric anaesthesia, little is known about its cardiovascular effects on the fetus. Invasive studies in human fetus are difficult to justify on ethical grounds and investigations of the effects of etomidate have therefore been performed on the newborn after caesarean delivery.

In the current study, our purpose was to determine the effects of etomidate on the cardiovascular system and acid–base status in the pregnant ewe and her fetus (a conventional model for studies of maternal–fetal physiology), following the administration of a single IV induction dose of etomidate and after an continuous IV infusion of 1 h preceded by a single IV induction bolus.

## Materials and methods

All procedures were approved by the Ethical Commission of Animal and Human Experimentation (Spanish Government, Authorization Number DARP465) under the auspices of the Ethical Commission of the Autonomous University of Barcelona.

Fourteen pregnant Lacaune breed sheep weighing (mean ± SD) 63 ± 8.5 kg were included in the study. Mean gestational age was 123 days (range 110–134 days; term 147–150 days).

### *Animal preparation*

The anaesthetic and surgical techniques used in our study were similar to those described by Andaluz et al. (2003) with some minor modifications. Sheep were premedicated with 0.01 mg/kg buprenorphine (Buprex, Schering-Plough Laboratories) and a single dose of 4 mg/kg propofol (Propofol Lipuro1%, Braun) was administered for anaesthesia induction through an 18-gauge polyurethane catheter (Vasocan, Braun) placed in the cephalic vein. The trachea was intubated with a 9–10 mm endotracheal tube, and anaesthesia maintained with 2–2.5% isoflurane (IsoFlo, Abbott Laboratories) in 100% oxygen through a semi-closed circular anaesthetic system. All animals were allowed to breathe spontaneously. An orogastric tube was inserted during the time the sheep was anaesthetized to prevent regurgitation and aspiration pneumonia.

All animals received an infusion of lactated Ringer's solution at a rate of 10 mL/kg/h during the perioperative period and IV antibiotic therapy (cephalexin, 20 mg/kg) was administered via the cephalic vein. The ewe's heart rate, pulse oximetry, respiratory rate and capnography were monitored during anaesthesia using a Datex Ohmeda Cardiocap II Monitor.

Each sheep was positioned in dorsal recumbency and the surgical field prepared aseptically. A midline laparotomy was performed and through a small hysterotomy the fetus was delivered partially to permit adequate exposure for insertion of a 71 cm, 14-gauge plain polyurethane catheter (Drucafix-Splittocan; Braun) into the carotid artery. The skin of the fetus was incised over the jugular vein and carotid artery. Fine dissection of the vessels and placement of the catheter was performed and the catheter was immediately heparinised and the blood pressure measured to ensure the functionality of the catheter. The skin incision was sutured and the fetus returned to the uterus.

A fetal carotid catheter was used for blood gas determination and for heart rate and fetal blood pressure measurement. Care was taken during surgery to minimize loss of amniotic fluid. The placenta and the uterus were closed as previously described (Andaluz et al., 2003). The fetal catheter was tunnelled subcutaneously through the ewe's flank, exteriorized and stored in a plastic pouch sewn to the skin of the flank. The laparotomy incision was closed in a routine manner.

The ewe's neck was prepared aseptically for catheter and tracheostomy tube placement. A semi-elliptical incision was made in the skin over the trachea and carotid artery. The artery was smoothly dissected for a 71 cm, 14-gauge plain polyurethane catheter (Drucafix-Splittocan; Braun) placement. The maternal carotid artery catheter was used for blood gases determination and for heart rate and blood pressure measurement. Tracheotomy was performed between the 4th and 5th tracheal rings, the endotracheal tube was removed and the tracheostomy tube was placed (Tracheostomy tube, smooth inner cannula, fenestrated soft-seal profile cuff; Smiths, Portex Limited). Then, the anaesthetic circuit was connected to the tracheostomy tube. Blood and secretions in the lumen of the tracheostomy were aspirated when needed during the postoperative period. Oxygen was administered during recovery from anaesthesia.

The animals were allowed to recover from surgery for 24 h before the experimental phase began. Ewe and fetal catheters were flushed every 8 h with heparinised saline solution to prevent occlusion. Animals were treated with subcutaneous buprenorphine 0.01 mg/kg every 12 h for pain control after surgery and 8 h prior to the experiment. Antibiotic therapy consisted of IV cephalexin 20 mg/kg every 12 h.

### *Experimental design*

Two independent studies were performed using two groups of seven ewes. In the first study, animals received a single IV bolus of 1 mg/kg etomidate for induction, while in the second study an IV bolus of 1 mg/kg etomidate was administered followed by a continuous infusion of 100 μg/kg/min etomidate for 1 h. The infusion was performed using a Medfusion 2010 Syringe Pump. A lipid emulsion formulation of etomidate (Etomidato Lipuro, Braun) was used.

Maternal and fetal heart rate and arterial blood pressure (systolic, diastolic and mean) and maternal respiratory rate and end tidal carbon dioxide ($EtCO_2$) were determined at different times using a Datex Ohmeda Cardiocap II Monitor. Fetal and maternal arterial blood samples were also taken at different times for acid–base variables evaluation using an i-STAT Portable Clinical Analyzer. Blood samples for acid–base determination were collected into a 1 mL heparinised insulin syringe and processed within 5 min. The appearance of adverse effects, such as salivation, regurgitation, myoclonus and apnoea, was recorded if present. Time to recovery from anaesthesia (standing) was also recorded.

Throughout the study period, sheep were kept warm in the operating theatre at and constant temperature. In the etomidate anaesthesia studies, all efforts were made to keep the sheep in sternal recumbency.

#### *Study 1*

Before the administration of the IV bolus of etomidate, control values were determined for both mother and fetus. Control values for heart rate, blood pressure, respiratory rate and $EtCO_2$ represent the means of three determinations taken at 15 min intervals, while control values for blood gases were measured only once.

After the 30 min control period and 5 min before etomidate treatment, the ewes received 100% oxygen via the tracheostomy tube. A single IV bolus of 1 mg/kg etomidate was then administered through the cephalic vein catheter and both maternal and fetal cardiovascular variables were measured at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420 and 480 min post-etomidate induction. Blood samples for acid–base status evaluation were taken simultaneously from mother and fetus at 5, 15, 30, 60, 120, 240 and 480 min after etomidate injection.

#### *Study 2*

As in Study 1, control blood samples were collected from both mother and fetus and oxygen therapy was started 5 min before etomidate anaesthesia. An initial IV bolus of 1 mg/kg etomidate was administrated followed immediately by a continuous IV infusion of 100 μg/kg/min etomidate for 1 h.

Cardiovascular variables were determined at 2, 5, 10, 15, 30, 45 and 60 min during etomidate infusion, and then at 5, 10, 15, 20, 30, 45, 60, 90,