

Changes in respiratory function following the intramuscular administration of etorphine to boer goats (*Capra hircus*)

P E Buss^a and D G A Meltzer^b

ABSTRACT

The physiological effects on respiratory function of etorphine (M99, Logos Agvet) (30 µg/kg) administered intramuscularly were determined in boer goats. The goats were habituated to the experimental procedures so that respiratory function could be determined while the animals stood quietly at rest. This enabled the physiological changes induced by etorphine to be measured and compared with those obtained before administration of the immobilising drug. The effectiveness of diprenorphine (M5050, Logos Agvet) (3 mg/1 mg etorphine) as an antagonist of the physiological changes induced by the etorphine treatment was also determined. Etorphine depressed respiratory function, which resulted in a decrease in PaO₂ and an increase in PaCO₂. These changes were limited and occurred as a result of decreases in respiratory minute volume and alveolar minute ventilation caused by a decrease in respiratory rate. The physiological shunt fraction did not change significantly but there was a significant decrease in percentage physiological dead space ventilation. It was not possible to determine how effectively diprenorphine reversed the respiratory effects due to etorphine.

Key words: *Capra hircus*, diprenorphine, etorphine, goats, respiratory function.

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INTRODUCTION

Etorphine, often in combination with either a sedative or tranquilliser, has been used extensively in the immobilisation and capture of African ungulates^{10,26}. Nevertheless, very little is known about the physiological responses of non-domestic artiodactyls either to these procedures or to the drug⁶. In most studies respiratory function has only been monitored once the animals have been immobilised. Thus, baseline data and physiological changes during the critical induction period are unknown. It is also difficult to differentiate between the drug-induced effects and the concurrent physiological effects due to capture and handling¹².

Etorphine acts stereospecifically with opioid receptors, inducing a conformational change, which in turn results in biochemical changes within the neuron^{3,23}. Etorphine acts as an agonist at both mu- and kappa-receptors. This results in a number of effects, including supraspinal

and spinal analgesia, euphoria, sedation and respiratory depression²³. Respiratory depression due to etorphine appears to be mediated by the mu₂-receptors⁴, and is primarily due to a direct effect on the brainstem respiratory centres, reducing their responsiveness to carbon dioxide. Etorphine also depresses the pontine and medullary centres that regulate respiratory rhythm and the responsiveness of the medullary respiratory centres to electrical stimulation. Large numbers of opioid receptors are found in the medullary areas believed to be important in ventilatory control¹³.

Diprenorphine is classified as a mixed antagonist, retaining some agonistic activity. As its action is much closer to that of an antagonist, it is routinely used as a reversing agent for etorphine^{16,26}. Diprenorphine can be administered intravenously or intramuscularly. If given intramuscularly it is reported to take 5 to 10 minutes to reverse the effects of etorphine, compared to a few seconds to 4 minutes if given intravenously¹.

Domestic goats have been used in experiments to evaluate the effects of etorphine on some respiratory and cardiovascular functions^{11,27}. Goats were

selected for this study, as they can be more easily handled under experimental conditions, are relatively small and are easily tamed. As a result, they are less likely to manifest restraint-induced physiological changes. Studies to date suggest that the goat is a suitable model to determine the physiological effects of drugs commonly used in the immobilisation of non-domestic artiodactyls^{11,12,18,27}.

We report here on part of a more extensive study that not only examined the effects of etorphine on respiratory function, but also recorded the effects of etorphine and etorphine combined with xylazine or azaperone on respiratory and cardiovascular function in goats.

The aims of the study were to:

- evaluate the effects on respiratory function of etorphine following intramuscular administration,
- evaluate the antagonist diprenorphine in its ability to reverse the effects on respiratory function induced by etorphine,
- measure baseline data under controlled conditions, from which the effects of etorphine in goats can be used to estimate the effects it may have in non-domestic artiodactyls.

MATERIALS AND METHODS

Animals

Eight non-pregnant female boer goats of a similar age and body mass were kept together in an enclosure. They were fed lucerne and concentrate pellets and water was provided *ad libitum*. Six animals from this herd were assigned to be used in the research procedures and 2 were kept as replacements to be used in the event of any losses. Before commencement of the study, each animal was examined clinically, and haematological and blood chemistry profiles were measured. Each goat was treated at the time of the clinical examination with 1 ml Ivermectin 1 % m/v (Ivomec injectable, Logos Agvet), administered subcutaneously. During the period of confinement, faecal flotations were performed from time to time on fresh samples collected randomly from the enclosure in which the goats were housed.

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To prevent the goats from becoming unduly distressed or excited, they were habituated to standing on a low research table while restrained by their horns during the following procedures: being handled, insertion of arterial and venous catheters, and the attachment of various other measuring devices. They were also conditioned to breathe into an attached face mask so that expired air samples could be collected.

Carotid relocation

About 2 months before the start of the trial, the left carotid artery of each goat was relocated surgically to a subcutaneous position in the neck to facilitate the collection of arterial blood samples, using the technique described by Butler⁵.

Preparation of trial procedures

One trial was done per day, in the morning. Food was withheld from the single selected animal for 17 hours and water for 2 hours before to the start of each trial. The goat was weighed. The neck was shaved on either side from immediately below the mandible to the level of the thoracic inlet. Long-acting penicillin (Peni L A Phenix, Logos Agvet) was administered intramuscularly.

The goat was placed standing on the research table, fastened to an overhead bar by a nylon rope tied around the base of its horns. An airtight face mask was placed over the nostrils and fixed in place with a crepe bandage. The animal was blindfolded, its ears were plugged with cotton wool, and the pinnae were folded back out of the way and fixed to the horns with adhesive tape. Electrocardiogram (ECG) leads were attached to prepared sites on the lateral surfaces of the legs, above the carpi and hocks. The ECG wave form was used primarily to monitor cardiac function during the insertion of the thermodilution catheter and during the trial. A thermometer probe was placed 10 cm into the rectum and fastened to the base of the tail with adhesive tape.

Catheterisation for blood-gas samples

Local anaesthetic (Lignocaine injection 2% , Bayer Animal Health) was injected subcutaneously at a site above the translocated carotid artery and over the jugular vein on the opposite side of the neck. After a skin incision had been made at each site an arterial catheter (20G Radial Artery Catheterization Set, Arrow Africa) was inserted into the translocated carotid artery and a percutaneous sheath introducer for the thermodilution catheter (Percutaneous Sheath Introducer Set with Side Port/Hemostasis Valve, Arrow

Africa) was inserted into the right jugular vein under aseptic conditions. Both were sutured to the skin to keep them in place. A thermodilution catheter (7 French gauge, Infusion port five lumen thermodilution catheter, Arrow Africa) was inserted through the percutaneous sheath introducer into the jugular vein and passed down through the right ventricle and into the pulmonary artery. The route taken by the catheter and progress of its insertion was monitored by viewing changes in blood pressure that took place in the jugular vein, right atrium, right ventricle and pulmonary artery on the screen of the vital signs monitor (DINAMAP™ PLUS Vital Signs Monitor Model 8720 plus Printer Module, CRITIKON, Johnson & Johnson) attached to it. The position of the end of the catheter in the pulmonary artery was standardised by inserting it with the balloon inflated until a wedge pressure was recorded. The balloon was then deflated. Once a goat had been prepared it was left to stand quietly for 10 minutes before the start of each trial.

Sampling

During the trial, samples and data were collected at 10-minute intervals, starting 25 minutes before injection of etorphine. These included mixed venous and arterial blood samples, expired and end-tidal (alveolar) air, respiratory rate and body temperature. These data were collected on 3 occasions before drug administration.

Blood-gas samples

The arterial blood sample was collected from the intra-arterial catheter in the carotid artery. A mixed venous blood sample was collected from the pulmonary artery using the distal lumen of the thermodilution catheter. All samples were collected anaerobically into heparin-treated glass syringes. The syringe was immediately capped, placed in an ice-bath and processed within 10 minutes. Both the arterial and mixed venous blood samples were analysed in a blood-gas apparatus (ABL 500, Medical Distributors Ltd).

Expired air

Expired air was collected over a period of 3 minutes through a 1-way valve from the face mask into in a 200 gm meteorological balloon (Totex Meteorological balloon, C.W. Price and Company). During collection of the expired air the respiration rate was counted. Immediately following the collection of the expired air, the balloon was sealed and a 50 ml mixed expired gas sample was collected from the neck of the balloon

into a glass syringe. This sample was processed in the blood-gas apparatus. The volume of expired air remaining in the balloon was measured in a spirometer. The temperature of the spirometer was recorded at the same time.

End-tidal air samples

The position of the trachea was palpated at the thoracic inlet and the overlying skin was marked with a black permanent marker on the tracheal midline. This site was infiltrated with 3 ml of 2% lignocaine. During the trial, a 1.2 × 38 mm hypodermic needle was inserted into the trachea at this site and end-tidal air samples were collected into a 50 ml glass syringe. The samples were immediately analysed in the blood-gas apparatus.

Drugs administered

Etorphine (30 µg/kg) was administered by deep intramuscular injection at time 0 minutes. The total volume of etorphine injectable solution was standardised at 2 ml using sterile water. A standard injection site 5 cm behind the wing of the ilium into the gluteal muscle on the right side of the animal was used. Each goat was considered to be immobilised when it assumed sternal recumbency and no longer responded to a painful stimulus caused by application of artery forceps across a coronary band. Diprenorphine (3 mg/1 mg etorphine) was administered intravenously 40 minutes after drug administration (PDA), i.e., after administration of the etorphine. All trials ended at 95 minutes PDA.

Calculation of derived variables

Respiratory minute volume_{BTPS}

The respiratory minute volume was assumed to be equivalent to the expired volume of air per minute. The volume of expired air was measured in a spirometer at ambient temperature, pressure and saturated with water vapour (ATPS). The volume at body temperature, ambient pressure and saturated with water vapour (BTPS) was calculated using standard formulae³⁰. All respiratory volumes measured at ATPS were reported and discussed at BTPS.

Tidal volume_{BTPS}

The respiratory minute volume was divided by the respiratory rate to give the tidal volume⁷.

Alveolar minute ventilation_{BTPS}

Alveolar ventilation is equivalent to tidal volume minus the dead space ventilation³². Dead space ventilation was calculated using the partial pressures of carbon

dioxide in the arterial blood and mixed expired air samples³². All volumes were measured at ATPS and converted to BTPS.

Physiological shunt fraction

The physiological shunt fraction expressed as a percentage of the cardiac output was calculated using the standard formula as reported by West²⁹. 'Ideal oxygen saturation' and thus 'ideal oxygen concentration of the end capillary blood' was calculated using the algorithm reported by Watney²⁸. No algorithm was available for goats. The algorithm indicated for sheep was found to be unsuitable for goats, as negative physiological shunt fractions resulted. The algorithm and constants indicated for cattle were therefore used²⁸.

Physiological dead space ventilation fraction

Physiological dead space ventilation was calculated and expressed as a percentage of the tidal volume²⁹.

Statistical analysis

Statistical analysis of the collated data was performed using the Statistical Analysis System (SAS[®], SAS Institute SA, Houghton). As the data were unbalanced owing to some missing observations, statistical analysis was performed using General Linear Models (GLM).

The dependent variable used was the variable determined for each time interval for the physiological variables examined (e.g. PaO₂, alveolar minute ventilation, etc.) for etorphine, i.e. within the drug. These included variables between the mean baseline value at rest (MBVR) and variables measured at any subsequent time interval. The class variable had 1 level, i.e. etorphine.

The covariable was the mean of the 3 values measured at -15, -10 and -5 min. when the goats were standing at rest, i.e. MBVR. In developing the GLM the square of MBVR (SQMBVR) was initially included as a second covariable to ensure that the relationship between MBVR and the dependent variable was linear and not a quadratic. As the relationship was found to be linear, SQMBVR was not used in the final model.

The GLM performed an initial *F*-test to determine whether the model provided a significant fit to the data. The covariable, as stated above, accounted for variation between the goats. Subsequently, a Fischer's test was used for pairwise comparisons between time intervals within treatments. The probability value for significance was set at $P \leq 0.05$. Data are presented graphically as the mean plus standard error (SE) (Figs 1–6).

RESULTS

Immobilisation

All goats became immobile within 5 minutes of drug administration. They went down into a sternal position and did not respond to painful stimuli. Administration of diprenorphine was followed by a brief period of increased activity in the goats during which they often defaecated and urinated. Thereafter they settled into a sternal position once again and appeared to be partially sedated although aware of their surroundings.

Blood gases and respiratory function

The PaO₂ decreased significantly and reached a minimum value 5 minutes after administration of etorphine. It then gradually increased until diprenorphine was given. These changes were mirrored by a rapid and significant rise in the PaCO₂ followed by a gradual decrease (Fig. 1). However, the PaCO₂ returned to its baseline value after 35 minutes. The arterial pH declined rapidly during the initial 5 minutes, and then underwent a gradual return to the baseline value during the remaining period of immobilisation (Fig. 2). Respiratory minute volume and alveolar minute ventilation both decreased significantly and reached minimum values 15 minutes after etorphine administration (Figs 3, 5). The decrease in respiratory minute volume was accompanied by significant changes in respiratory rate rather than in tidal volume (Fig. 4). The respiratory minute volume and alveolar minute ventilation increased over time until the diprenorphine was administered.

The physiological shunt fraction did not change significantly during the period of immobilisation. The percentage physiological dead space ventilation decreased significantly within 5 minutes of drug administration and did not change thereafter until the diprenorphine was administered (Fig. 6).

The administration of diprenorphine was followed by a return of the PaO₂ and arterial pH values to their respective baseline values (Figs 1, 2). There was an immediate, although temporary, rise in the respiratory minute volume, with increases in both respiratory rate and tidal volume (Figs 3, 4). The alveolar minute ventilation returned to its baseline value within 5 minutes and subsequently did not change significantly (Fig. 5). The physiological dead space ventilation fraction, despite an initial increase for 20 minutes, remained significantly lower than its baseline value until the end of the trial (Fig. 6).

DISCUSSION

The significant decrease in the PaO₂ and increase in the PaCO₂ within 5 minutes of administration of the etorphine was not unexpected. Similar results have been reported when goats were administered 0.04 mg/kg of etorphine intramuscularly¹². The decrease in PaO₂ and increase in PaCO₂ followed significant decreases in respiratory minute volume and alveolar minute ventilation, which were the result of a decrease in respiratory rate rather than a change in tidal volume. The percentage physiological shunt did not change significantly and therefore did not contribute to the changes observed in the blood gases. During the same period, the percentage physiological dead space ventilation decreased and could be expected to have resulted in an increase in PaO₂ and a decrease in PaCO₂.

Respiratory depression is reported to be the principal toxic effect of the opioids in immobilised animals, with sensitivity to the drugs varying between species and individuals within species. It may result in severe hypoxia, hypercapnoea and progressive acidosis^{9,26}. Respiratory depression has been reported in Equidae, including the Mongolian horse (*Equus przewalskii*), and Grevy's zebra (*Equus grevyi*)¹. It has also been reported in domestic cattle (*Bos taurus*) and bighorn sheep (*Ovis canadensis*)¹, bears¹⁰ and the monkey, dog, cat and rat².

Impala immobilised with the opioids A-3080 (80.7 µg/kg) or carfentanil (68.8 µg/kg) administered intramuscularly, developed apparent hypoventilation soon after immobilisation, based on measurements of respiration rate, relative oxygen saturation and total serum carbon dioxide¹⁴. The respiratory volumes were not measured. Immobilisation of scimitar-horned oryx (*Oryx dammah*) with etorphine in combination with acepromazine or xylazine resulted in a fall in arterial oxygen tension, mild hypoxaemia and hypercapnoea, but did not cause respiratory acidosis²¹.

Immobilisation of adult Saanen goats with etorphine (70 µg/kg) and acepromazine (0.2 mg/kg) is reported to cause a decrease in respiratory rate and an increase in airway resistance. This was attributed to a decrease in lung volume due to the animals assuming sternal recumbency¹⁸. Intramuscular administration of etorphine in domestic goats premedicated with either triflupromazine or triflupromazine and atropine resulted in a decrease in respiratory rate²⁷. Etorphine (20 µg/kg) given intravenously to adult mixed-breed goats produced a significant bradypnoea with maximum depression occurring at 2.5 minutes after administra-

tion. Thereafter, respiratory rates gradually increased, returning to normal within 45 minutes¹¹.

Etorphine has an inhibitory effect on the brain stem respiratory centres, reducing their sensitivity to carbon dioxide and results in a decreased respiratory drive^{13,23}. Although opioids are reported to depress all phases of respiration, their primary effect is a reduction of the rate of breathing¹³, as was recorded in this investigation (Fig. 4). Heard *et al*¹¹ reported that goats injected with etorphine intravenously developed a significant bradypnoea. Etorphine administered to goats premedicated with either triflupromazine or triflupromazine and atropine, resulted in a decrease in respiratory rate²⁷. Similar results are reported in Saanen goats given etorphine plus acepromazine¹⁸. Tidal volume, respiratory minute volume and alveolar minute ventilation were not measured in these studies.

The respiratory volumes in the immobilised goats may also have been depressed by a number of factors other than inhibition of the respiratory centres by etorphine. These include: a change in body position from standing to sternal recumbency, obstruction of the upper airway resulting in an increased resistance to airflow^{17,31}, or development of ruminal bloat¹⁷.

There is a reported rise in intraruminal and intraperitoneal pressure in cattle that assume sternal recumbency, which changes the relative position of the diaphragm, resulting in an increase in respiratory resistance²⁵. Increased measured airway resistance was reported when goats assumed sternal recumbency after immobilisation with etorphine and acepromazine¹⁸.

The effects that the change in body position had on respiratory function in this investigation were not determined. The goats assumed sternal recumbency after administration of etorphine, and this position was maintained in all the immobilised animals. There were no differences in the postural changes that occurred and thus the effects on respiratory function were similar in all cases.

The heads of the goats were supported in an elevated position and the same relative positions of the head, neck and thorax were maintained throughout each trial period. No significant change in airway resistance could have occurred¹⁵. Maintaining the head and neck position also allowed unobstructed passage of gas produced in the rumen and prevented development of ruminal bloat.

The initial etorphine-induced depression of respiratory function in the immo-

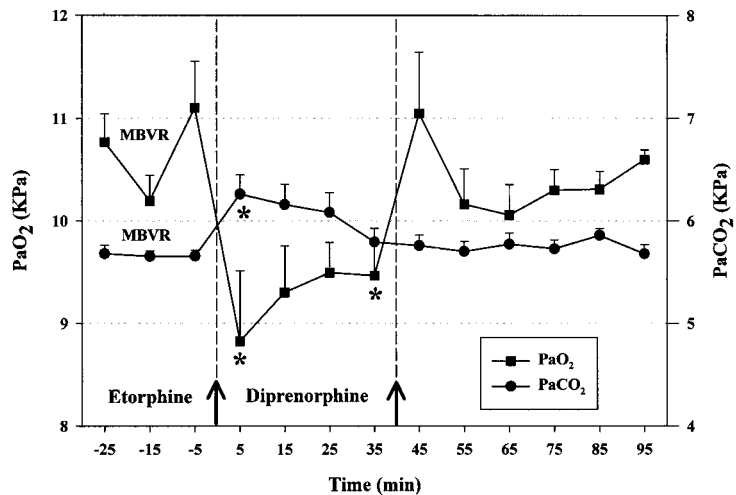


Fig. 1: Mean arterial PaO₂ and PaCO₂ in goats treated with etorphine. Error bar = 1 SE. MBVR = mean baseline value at rest. Asterisks indicate statistically significant differences ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

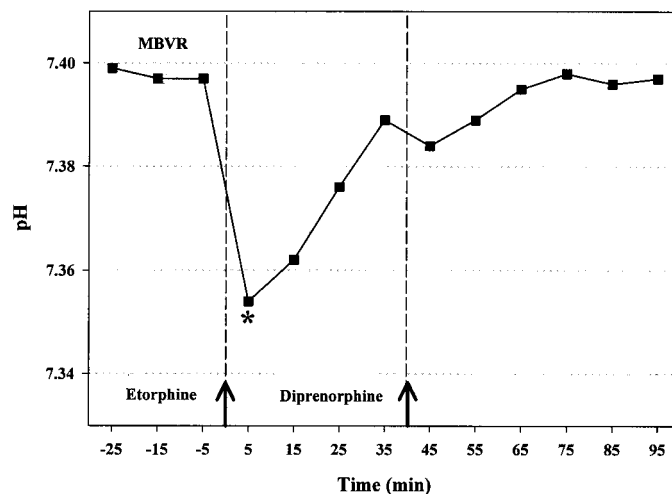


Fig. 2: Mean arterial pH in goats treated with etorphine. MBVR = mean baseline value at rest. The asterisk indicates a statistically significant difference ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

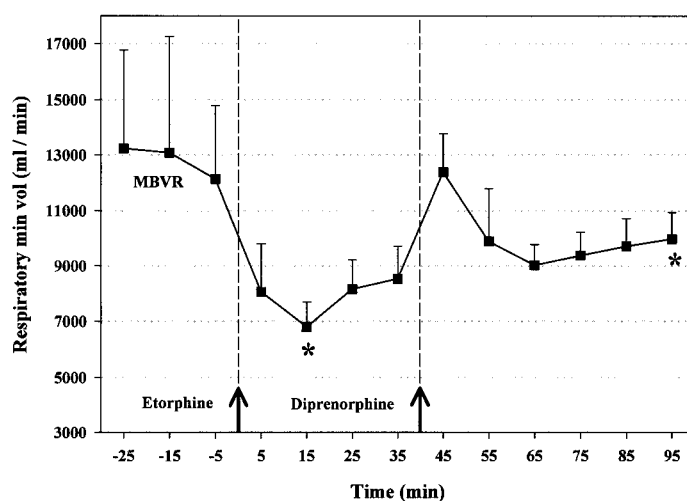


Fig. 3: Mean respiratory minute volume in goats treated with etorphine. Error bar = 1 SE. MBVR = mean baseline value at rest. Asterisks indicate statistically significant differences ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

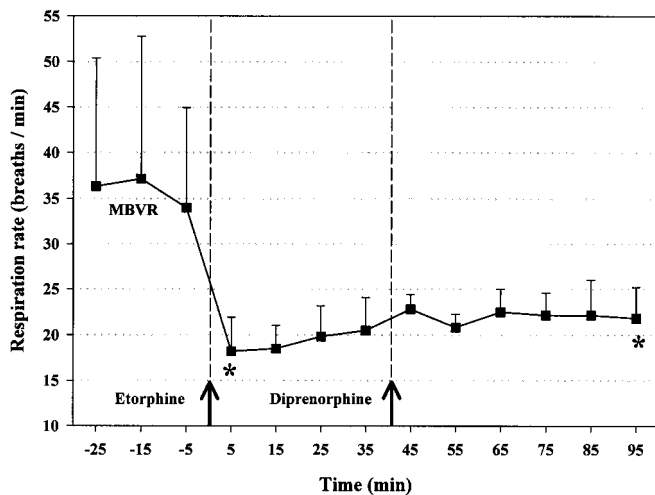


Fig. 4: Mean respiratory rate in goats treated with etorphine. Error bar = 1 SE. MBVR = mean baseline value at rest. Asterisks indicate statistically significant differences ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

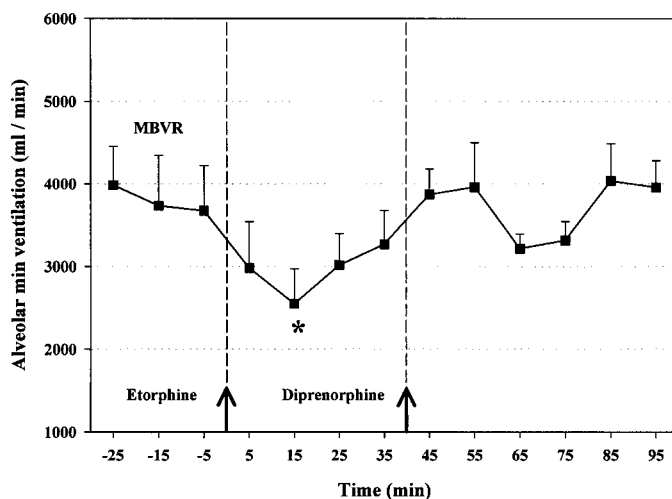


Fig. 5: Mean alveolar minute ventilation in goats treated with etorphine. Error bar = 1 SE. MBVR = mean baseline value at rest. The asterisks indicates a statistically significant difference ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

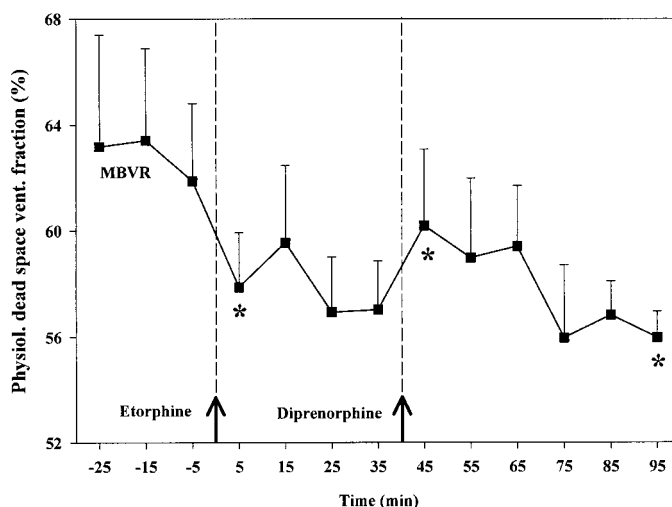


Fig. 6: Mean physiological dead space ventilation fraction in goats treated with etorphine. Error bar = 1 SE. MBVR = mean baseline value at rest. Asterisks indicate statistically significant differences ($P \leq 0.05$) between MBVR and the signalled mean value. Arrows indicate times at which etorphine and diprenorphine were injected.

bilised goats was followed by gradual recovery. This improvement in respiratory function may have resulted from the hypoxic stimulation of the chemoreceptors that are reported to remain effective even when opioids have suppressed the responsiveness of the respiratory centre to carbon dioxide²². Although stimulation of respiration by the peripheral chemoreceptors is reported to become marked only at a PaO_2 of between 2.7 to 5.3 KPa in humans⁸ and below 8.0 KPa in horses¹⁷, it appears that this stimulus may be more significant in goats. It has been shown that denervation of the carotid body in goats results in some hypoventilation, hypoxaemia and hypercapnoea¹⁷. In addition to these changes, it is likely that reduction of the pharmacodynamic effects of etorphine as a result of its metabolism also permitted improvement in respiratory function over time.

The onset of the effects of etorphine in wildlife is reported to take place 2–8 minutes after intramuscular administration. The peak effects, depending on the rate of absorption, follow in 15–30 minutes. The duration of effect is approximately 1 hour²⁶. In goats, Heard *et al*¹¹ reported that 0.02 mg/kg of etorphine administered intravenously resulted in a maximum depression of respiratory rate within 2.5 minutes. The respiratory rate then gradually returned to within normal limits by 45 minutes PDA.

The decrease in physiological dead space ventilation following the administration of etorphine was an unexpected finding. Although the cause of this decrease cannot be determined from the results of this trial, some possible causes can be suggested. These include a decrease in alveolar dead space due to improved alveolar perfusion. Etorphine is reported to increase systemic mean arterial blood pressure owing to centrally-mediated activation of sympathetic tone²⁴. It may also result in increases in pulmonary arterial pressure. A second possible cause is hypoventilation (Fig. 3) induced by administration of etorphine. Hypoventilation is reported to result in a reduction in the functional anatomical dead space in humans, owing firstly to a more streamlined or laminar flow of gas through the bronchi, and secondly to mixing of all gases lying below the carina by the heartbeat²⁰. Thirdly, less inspired air is delivered to alveoli with minimal circulation as a result of a slower respiration rate and, therefore, an increased duration of inspiration¹⁹.

Diprenorphine administered intravenously is reported to antagonise the effects of etorphine rapidly¹. In this study it was not possible to determine to what

degree it reversed the respiratory depressant effects of etorphine, as there was a gradual recovery of respiratory function and the PaCO₂ had returned to its baseline value by the time the diprenorphine was administered. The continued depression of the respiratory rate following the administration of the diprenorphine (Fig. 4) was possibly due to the fact that diprenorphine is a mixed opioid antagonist, retaining some agonist activity²⁶. It is also possible that the low respiratory rate may have been caused by residual etorphine activity.

CONCLUSIONS

Goats proved to be suitable animals in which to determine the physiological changes that occur in respiratory function following the administration of etorphine. They were amenable to being handled while restrained on the research table and rapidly became habituated to and tolerant of the experimental procedures. It is considered that any adrenergic response in the goats before administration of etorphine was effectively minimised. Following each trial, the goats rapidly recovered without significant side-effects.

The administration of etorphine to the goats resulted in respiratory depression as reported in various other immobilised animal species^{9,26}. The decrease was due primarily to a slowing of respiratory rate, rather than a reduction in tidal volume. Changes to the percentage physiological shunt and dead space ventilation do not appear to contribute significantly to the decrease in PaO₂ and increase in PaCO₂ induced by the intramuscular administration of etorphine.

It was not possible to determine how effective diprenorphine was in reversing the depressant effects of etorphine on respiratory function.

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