THE PHARMACODYNAMICS OF ETORPHINE, AND ITS COMBINATION WITH XYLAZINE OR AZAPERONE IN BOER GOATS (*Capra hircus*)

by

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CONTENTS

LIST OF ABBREVIATIONS X

LIST OF TABLES XIII

LIST OF FIGURES XV

1. INTRODUCTION 1

2. LITERATURE REVIEW 3

2.1 ETORPHINE 3

2.1.1 Introduction 3

2.1.2 Pharmacological effects 4

2.1.2.1 Respiratory function 5

2.1.2.2 Cardiovascular function 7

2.2 XYLAZINE 10

2.2.1 Introduction 10

2.2.2 Pharmacological effects 12

2.2.2.1 Respiratory function 12

2.2.2.2 Cardiovascular function 16

2.3 AZAPERONE 19

2.3.1 Introduction 19

2.3.2 Pharmacological effects 21

2.3.2.1 Respiratory function 21

2.3.2.2 Cardiovascular function 22

2.4 ATIPAMEZOLE 23

2.4.1 Introduction 23

2.4.2 Pharmacological effects 24

2.5 DIPRENORPHINE 26

2.5.1 Introduction 26

2.5.2 Pharmacological effects 26

3. MATERIALS AND METHODS 27

3.1 STUDY ANIMALS 27

3.1.1 Introduction 27

3.1.2 Carotid artery translocation 27

3.1.3 Clinical examination 28

3.2 TRAINING OF THE GOATS 29

3.2.1 Introduction 29

3.2.2 Training 29

3.2.3 Research table 30

3.3 CLINICAL TRIALS 30

3.3.1 Introduction 30

3.3.2 Housing of goats 32

3.3.3 Preparation prior to each trial 32

3.3.3.1 Research room 32

3.3.3.2 Recording of data 32

3.3.3.3 Initial preparation of the goat 33

3.3.3.4 Preparation of monitoring equipment 33

3.3.3.5 Final preparation of the goat 35

3.3.4 Collection of data and samples 37

3.3.4.1 Introduction 37

3.3.4.2 Thermodilution cardiac output determinations 38

3.3.4.3 Collection of blood samples 38

3.3.4.4 Expired air samples 39

3.3.4.5 End expired air samples 40

3.3.4.6 Room air samples and temperature 40

3.4 CALCULATION OF DERIVED VARIABLES 40

3.4.1 Respiratory minute volume $_{(BTPS)}$ 40

3.4.2 Tidal volume $_{(BTPS)}$ 41

3.4.3 Alveolar minute ventilation $_{(BTPS)}$ 42

3.4.4 Physiologic shunt fraction 43

3.4.5 Physiologic dead space ventilation fraction 45

3.4.6 Total peripheral resistance 45

3.4.7 Stroke volume 46

3.4.8 Oxygen consumption index 46

3.5 STATISTICAL ANALYSIS OF DATA 47

3.5.1 General linear model 48

4. RESPIRATORY FUNCTION 50

4.1 RESULTS 50

4.1.1 Etorphine 51

4.1.1.1 Immobilization 51

4.1.1.2 Recovery 52

4.1.2 Etorphine / xylazine 52

4.1.2.1 Immobilization 52

4.1.2.2 Recovery 53

4.1.3 Etorphine / azaperone 54

4.1.3.1 Immobilization 54

4.1.3.2 Recovery 55

4.1.4 Comparisons between the three treatments 56

4.1.4.1 Induction, immobilization and recovery 56

Arterial PaO_2 56

Arterial $PaCO_2$ 57

Arterial pH 59

Respiratory minute volume 60

Respiratory rate 61

Tidal volume 61

Alveolar ventilation 62

Physiologic shunt fraction 63

Physiologic dead space ventilation fraction 64

4.2 DISCUSSION 65

4.2.1 Introduction 65

4.2.2 Etorphine 67

4.2.3 Etorphine / xylazine 71

4.2.4 Etorphine / azaperone 77

5. CARDIOVASCULAR FUNCTION 80

5.1 RESULTS 80

5.1.1 Etorphine 80

5.1.1.1 Immobilization 80

5.1.1.2 Recovery 81

5.1.2 Etorphine / xylazine 81

5.1.2.1 Immobilization 81

5.1.2.2 Recovery 81

5.1.3 Etorphine / azaperone 82

5.1.3.1 Immobilization 82

5.1.3.2 Recovery 82

5.1.4 Comparisons between the three treatments 83

5.1.4.1 Induction, immobilization and recovery 83

Systemic mean arterial blood pressure 83

Total peripheral resistance 84

Cardiac output 85

Heart rate 87

Stroke volume 87

5.2 DISCUSSION 88

5.2.1 Introduction 88

5.2.2 Etorphine 90

5.2.3 Etorphine / xylazine 92

5.2.4 Etorphine / azaperone 95

6. OXYGEN CONSUMPTION 97

6.1 RESULTS 97

6.1.1 Etorphine 97

6.1.1.1 Immobilization 97

6.1.1.2 Recovery 97

6.1.2 Etorphine / xylazine 98

6.1.2.1 Immobilization 98

6.1.2.2 Recovery 98

6.1.3 Etorphine / azaperone 99

6.1.3.1 Immobilization 99

6.1.3.2 Recovery 99

6.1.4 Comparisons between the three treatments 100

6.1.4.1 Induction, immobilization and recovery 100

Oxygen consumption index 100

Arterial oxygen concentration 101

Venous oxygen concentration 102

Arterial haemoglobin concentration 103

Arterial oxygen saturation 104

6.2 DISCUSSION 105

6.2.1 Introduction 105

6.2.2 Etorphine 107

6.2.3 Etorphine / xylazine 108

6.2.4 Etorphine / azaperone 110

7. GENERAL DISCUSSION AND CONCLUSIONS 113

SUMMARY 118

REFERENCES 120

APPENDICES 134

Appendix A : Respiratory function : Tables of statistical probabilities 134

Appendix B : Cardiovascular function : Tables of statistical probabilities 155

Appendix C : Oxygen consumption : Tables of statistical probabilities 168

LIST OF ABBREVIATIONS

Respiratory function

V_T	Tidal volume
T	Respiratory rate
V_D	Dead space
PaO_2	Partial pressure of oxygen in arterial blood
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
P_ECO_2	Partial pressure of carbon dioxide in expired air
S	Arterial blood oxygen saturation
P_AO_2	Partial pressure of oxygen in alveolar air
CiO_2	Ideal oxygen concentration of end capillary blood
V_{DPHYS}	Physiologic dead space
CaO_2	Concentration of oxygen in arterial blood
CvO_2	Concentration of oxygen in mixed venous blood
$\dot{V}_E$	Respiratory minute volume
$\dot{V}_A$	Alveolar minute ventilation
$\dot{Q}_{PS}$	Physiologic shunt blood flow per minute

Cardiovascular function

[Hb]a	Arterial haemoglobin concentration
TPR	Total peripheral resistance
MAP	Systemic mean arterial pressure
RAP	Right atrial pressure
SV	Stroke volume
HR	Heart rate
$\dot{Q}$	Cardiac output

Oxygen consumption

OCI	Oxygen consumption index
$\dot{V}O_2$	Oxygen consumption

Miscellaneous

ATPS	Ambient temperature, ambient pressure and saturated with water vapour
BTPS	Body temperature, ambient pressure and saturated with water vapour
PDA	Post drug administration. Time elapsed since the administration of the immobilizing drugs
MBVR	Mean baseline value at rest

e	Etorphine
ex	Etorphine / xylazine
ea	Etorphine / azaperone
PRU	Peripheral resistance units
T	Temperature
P_b	Barometric pressure
P_{H_2O}	Vapour pressure of water
B	Body
S	Spirometer
BW	Body weight

LIST OF TABLES

Materials and methods

Table 3.1 The order of treatment allocation to the goats. 31

Table 3.2 The three treatments administered to the goats 31

Respiratory function

Table 4.1 The mean $PaCO_2$, PaO_2 and arterial pH of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation) 66

Table 4.2 The mean minute respiratory volume, respiration rate and tidal volume of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation) 66

Table 4.3 The mean alveolar minute ventilation, physiologic shunt fraction and physiologic dead space ventilation fraction of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation) 67

Cardiovascular function

Table 5.1 The mean systemic mean arterial blood pressure and total peripheral resistance of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation) 89

Table 5.2 The mean cardiac output, heart rate and stroke volume of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation) 90

LIST OF FIGURES

Respiratory function

Figure 4.1 Mean arterial PaO_2 in goats treated with different immobilizing drugs . . . 56

Figure 4.2 Mean arterial $PaCO_2$ in goats treated with different immobilizing drugs . . 57

Figure 4.3 Mean arterial pH in goats treated with different immobilizing drugs 58

Figure 4.4 Mean respiratory minute volume in goats treated with different immobilizing drugs 59

Figure 4.5 Mean respiratory rate in goats treated with different immobilizing drugs . 60

Figure 4.6 Mean tidal volume in goats treated with different immobilizing drugs 61

Figure 4.7 Mean alveolar minute ventilation in goats treated with different immobilizing drugs 62

Figure 4.8 Mean physiologic shunt fraction in goats treated with different immobilizing drugs 63

Figure 4.9 Mean physiologic dead space ventilation fraction in goats treated with different immobilizing drugs 64

Cardiovascular function

Figure 5.1 Mean systemic mean arterial blood pressure in goats treated with different immobilizing drugs 84

Figure 5.2 Mean total peripheral resistance in goats treated with different immobilizing drugs 85

Figure 5.3 Mean cardiac output in goats treated with different immobilizing drugs .. 86

Figure 5.4 Mean heart rate in goats treated with different immobilizing drugs 87

Figure 5.5 Mean stroke volume in goats treated with different immobilizing drugs .. 88

Oxygen consumption

Figure 6.1 Mean oxygen consumption index in goats treated with different immobilizing drugs 101

Figure 6.2 Mean arterial oxygen concentration in goats treated with different immobilizing drugs 102

Figure 6.3 Mean venous oxygen concentration in goats treated with different immobilizing drugs 103

Figure 6.4 Mean arterial haemoglobin concentration in goats treated with different immobilizing drugs 104

Figure 6.5 Mean arterial oxygen saturation in goats treated with different immobilizing drugs 105

CHAPTER 1

INTRODUCTION

Chemical agents including etorphine in combination with either xylazine or azaperone have been used extensively in the immobilization and capture of African ungulates[44,104]. Despite this, very little is known about the physiological responses of non-domestic artiodactyls to either these procedures or the drugs used[23]. In most studies the monitoring of respiratory and cardiovascular function has only taken place once the animals have become immobilized. 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 handling[50].

The study was undertaken to:

a) Evaluate and compare the effects on respiratory and cardiovascular function of the immobilizing drug treatments: etorphine; etorphine and xylazine; etorphine and azaperone, after intramuscular administration.

b) Evaluate the antagonists, diprenorphine and atipamezole, in their ability to reverse the effects on respiratory and cardiovascular function induced by the immobilizing drug treatments.

c) Measure baseline data under controlled conditions, from which the effects of immobilizing drugs can be estimated and to compare these effects one with the other.

Goats were selected for this study, as they can be more easily handled under experimental conditions, are a relatively small size and are easily tamed. As a result, they are less likely to manifest restraint-induced physiological changes. Studies to date, suggest that goats are a suitable animal in which to determine the physiological effects of immobilizing drugs commonly used in the immobilization of non-domestic artiodactyls[49,50,77,106].

CHAPTER 2

LITERATURE REVIEW

2.1 ETORPHINE

2.1.1 Introduction

Etorphine is a potent, semi-synthetic opioid derived from thebaine, one of the principle alkaloids of opium. Its chemical structure is 6,14-endoetheno-7alpha-(2-hydroxy-2-pentyl)-tetrahydro-oripavine hydrochloride[59,104].

Etorphine administered intramuscularly, usually results in rapid sedation, immobilization and analgesia in the Equidae, Ursidae, Cervidae and Bovidae[2]. It is commonly used for the immobilization and capture of African ungulates[104]. Etorphine can be used alone or in combination with tranquillizers or sedatives to enhance its effects[58]. Azaperone and alpha$_2$-agonists like xylazine, detomidine, or medetomidine are the most commonly used drugs for this purpose[44]. The actions of etorphine can be reversed by opioid antagonists, which include diprenorphine, nalorphine, naloxone and naltrexone[2,12,44,101].

Harthoorn[45], reports that the onset of effects following a standard dose of etorphine, is approximately four minutes. Peak effects, depending on the rate of absorption, usually occur within 15 to 30 minutes and last for approximately one hour. In juvenile African elephants (*Loxodonta africana*), peak serum concentrations of etorphine were found to occur at 30 minutes

after injection and then to decline steadily thereafter. The half-life was calculated to be 66 minutes[58].

The major route of excretion of etorphine is in the faeces[25], via the bile[43]. Only a small proportion is excreted by the kidneys. Most opioids are eliminated in the urine. Partial reabsorption of etorphine occurs in the intestinal tract[44].

2.1.2 Pharmacological effects

Opioid receptors are found within many different tissues in the body, including the brain and the spinal cord. These respond to endogenous morphine-like substances (i.e. enkephalins, dynorphines and endorphins), but will also bind with exogenous compounds, including etorphine. There are at least three types of opioid receptors:

a) Mu-receptors, of which there are two subtypes: mu_1 and mu_2

b) Kappa-receptors. Three subtypes have been described: $kappa_1$, $kappa_2$ and $kappa_3$

c) Delta-receptors[91] .

Etorphine acts stereospecifically with the receptor, inducing a conformational change, which in turn results in biochemical changes within the neuron[12]. 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 depression[91].

2.1.2.1 Respiratory function

Respiratory depression due to etorphine appears to be mediated by the mu_2-receptors[15] and is due primarily to a direct effect on the brainstem respiratory centers, reducing their responsiveness to carbon dioxide. Etorphine also depresses the pontine and medullary centers which regulate respiratory rhythmicity and the responsiveness of the medullary respiratory centers to electrical stimulation. Large numbers of opioid receptors are found in the medullary areas believed to be important in ventilatory control[59].

Respiratory depression is reported to be the principle toxic effect of the opioids in immobilized animals, with sensitivity to the drugs varying between species and individuals within species. It may result in severe hypoxia, hypercapnoea and progressive acidosis[43,104].

Hypoxaemia is reported in juvenile elephants immobilized with a drug combination of etorphine plus azaperone. It was suggested that this follows the respiratory depressant effect of etorphine and the fact that the animals were lying in lateral recumbency during the period of immobilization[103].

Impala immobilized with the opioids A-3080 (80.7 µg/kg) or carfentanil (68.8 µg/kg) administered intramuscularly, developed apparent hypoventilation soon after immobilization. This is based on measurements of respiration rate, relative oxygen saturation and total serum carbon dioxide[62]. The respiratory volumes were not measured.

The immobilization of scimitar horned oryx (*Oryx dammah*) with etorphine in combination with acepromazine or xylazine or both, administered intramuscularly by dart at various dose rates, resulted in a fall in arterial oxygen tension, a mild hypoxaemia (less than 80 mm Hg) and hypercapnoea (greater than 50 mm Hg), but did not cause respiratory acidosis[83]. Fallow deer (*Dama dama*) given these similar drug combinations, frequently exhibit irregular and shallow respiration, hypoxaemia and acidaemia[84].

Respiratory depression is reported in Equidae, including the Mongolian horse (*Equus przewalskii*) and Grevy`s zebra (*Equus grevyi*)[2]. It has also been reported in domestic cattle (*Bos taurus*) and Bighorn sheep (*Ovis canadensis*)[2]. It is common in bears[44].

Respiratory depression has also been reported in the monkey, dog, cat and rat[10]. A combination of etorphine and acepromazine produced a marked decrease in respiratory rate, and arterial blood oxygen tension; and mild respiratory acidosis in horses and ponies. The administration of diprenorphine, a mixed antagonist to etorphine, results in an increase in respiratory rate and a return of arterial oxygen and carbon dioxide tensions toward control levels[12,51,73].

One of the most dramatic changes associated with immobilization of adult Saanen goats with etorphine (70 µg/kg) and acepromazine (0.2 mg/kg), was a decrease in respiration rate. It was found that immobilization also resulted in an increase in airway resistance. This was attributed to a decrease in lung volume due to the animals assuming sternal recumbency[77].

The intramuscular administration of etorphine in domestic goats premedicated with either triflupromazine or triflupromazine and atropine, resulted in a decrease in respiration rate. This

lasted for up to 30 minutes and then it gradually increased. After a period of 40 minutes, however, it had not reach the pre-immobilization values[106].

Etorphine (20 μg/kg) given intravenously to adult mixed-breed goats produced a significant bradypnea with maximum depression (13 ± 3 breaths/minute) occurring at 2.5 minutes after administration. Thereafter, respiration rates gradually increased returning to normal within 45 minutes[49].

2.1.2.2 Cardiovascular function

The effect of etorphine on cardiovascular function appears to depend on the animal species in which it is used and the other drugs with which it may be combined[44]. Etorphine produces a bradycardia and an arterial hypotension in a number of smaller animal species. However, in some large species a tachycardia has been observed. An explanation for this difference is unclear[15].

Etorphine has been found to cause a pronounced tachycardia and increased blood pressure in the Equidae, including the domestic horse, Mongolian horse and Grevy's zebra[2,43]. These changes are probably caused by increased activity in the peripheral sympathetic nervous system, leading to increases in the rate and force of contraction of the heart and vasoconstriction. The site/s of action of etorphine in inducing sympathoadrenal stimulation have not been established[73]. It has been suggested that acepromazine moderates etorphine induced increases in blood pressure due to its $alpha_1$-adrenoceptor blocking properties[11].

Hypertension due to etorphine has also been reported in swine and a white rhinoceros[71]. Tachycardia and increased blood pressure has been reported in elephants immobilized with etorphine[44]. Etorphine is reported to cause bradycardia and hypotension in monkeys, dogs, cats and rats[10]. In domestic cattle findings differ from these species, and etorphine is reported to result in either a hypotension with bradycardia[44] or a hypertension with tachycardia[2]. In artiodactyls changes are more often seen at high doses when blood pressure tends to decline and a bradycardia is sometimes seen, more often at high doses[44]. Hypertension and an initial tachycardia are consistent findings in impala immobilized with the opioid narcotic A-3080 (80.7 µg/kg) or carfentanil (68.8 µg/kg) administered intramuscularly[62].

Very little alteration to heart rate was measured in scimitar horned oryx immobilized with etorphine in combination with acepromazine or xylazine or both, but systemic arterial pressure and pulmonary arterial pressure fell during the first hour[83]. Fallow deer immobilized with the same drug combinations show a continual gradual fall in heart rate and a slight tendency for the systemic arterial pressure to fall during the early stages of immobilization. Pulmonary arterial pressure was raised[84].

In domestic goats given triflupromazine and then immobilized with etorphine intramuscularly 15 minutes later, heart rates remained stable and within acceptable levels during the immobilization period of 70 minutes. In goats that were premedicated with atropine as well as triflupromazine, the heart rate had increased significantly after 15 minutes. Following the administration of the etorphine, the heart rate gradually decreased for 20 minutes, then increased and remained stable[106].

Etorphine (20 µg/kg) given intravenously to adult mixed-breed goats appeared to cause bradycardia, however, these changes were not statistically significant[49]. It is possible that the bradycardia observed in some goats was due to an arterial baroreceptor-mediated response to acute hypertension. Systolic, diastolic and mean systemic arterial pressures were significantly elevated with peak effects at 2.5 minutes after drug administration. These pressures then slowly declined but were still significantly elevated at 120 minutes after the administration of the etorphine[49].

Hypertension resulted in mixed breed and Nubian goats given etorphine in incremental doses of 5, 10, 20 and 40 µg/kg, intramuscularly. As the cardiac output remained the same and the total peripheral resistance increased, it was suggested that there was a terminal arterial and arteriolar constriction secondary to increased sympathetic nervous system activity[50].

2.2 XYLAZINE

2.2.1 Introduction

The chemical structure of xylazine is 2(2,6-dimethylphenylamine)-4-H-5,6-dihydro-1,3-thiazine hydrochloride[13,33]. Xylazine has synergistic properties when used in combination with etorphine. It reduces the dose required to produce immobilization, decreases induction time and results in better muscle relaxation. These factors have resulted in xylazine being often used in conjunction with etorphine in the immobilization of wild animals[13,104]. Its marked hypnotic action in all animals results in a dose-dependent state of sleep, but not in anaesthesia, as external stimuli are able to interrupt this unconscious state[53]. Antagonists including yohimbine, idazoxan, tolazoline or atipamezole can be used to reverse the sedative effects of xylazine[33,104].

Xylazine is a potent agonist of alpha$_2$-adrenoceptors in both neuronal and non-neuronal tissues. As well as alpha$_2$-adrenoceptor activity, xylazine has some alpha$_1$-adrenoceptor effects[34]. Due to effects on the central nervous system, xylazine causes sedation, analgesia and hypothermia. Cardiovascular effects include bradycardia and hypotension together with a minor decrease in respiratory rate[13,78,104]. Initial reports, suggest that xylazine does not show any selectivity for the alpha$_2$-adrenoceptor subtypes A, B, C and D[99].

Xylazine is rapidly absorbed, the half-life of absorption is 2.8 to 5.4 minutes[31] after an intramuscular injection and reaches its highest levels in the brain and kidney[67]. It's bioavailability following intramuscular administration is reported to range from 52% to 90% in the dog, 17% to 73% in the sheep, and 40% to 48% in the horse. It is rapidly metabolized with

approximately 20 metabolites being recognized. The primary degradation of xylazine is dependent on a functional liver[13]. The half-life of elimination ranges from 23 minutes in sheep to 50 minutes in horses[33]. In cattle it is difficult to relate the short half-life of xylazine (36.5 minutes) with some of the reported sustained clinical effects, e.g. polyuria (five hours), hyperthermia (18 hours), hypothermia (24 hours), prostration after a high dose (36 hours), and diarrhoea (12 to 24 hours) after injection[13]. The sensitivity of cattle to xylazine is also not explained by the plasma kinetics of the drug[33]. The lack of correlation between xylazine plasma concentration and its pharmacological effects in cattle may suggest that one or a number of long-acting metabolites are rapidly produced[31].

The effects of xylazine depend on the species, dose and route of administration. Intravenous xylazine results in maximal sedation within 6 to 6.5 minutes in the horse and within 3 to 5 minutes in dogs and cats. Following intramuscular administration, sedation is observed within 15 to 20 minutes in horses and 10 to 15 minutes in dogs and cats. Sedation appears to be dose dependent; it lasts approximately 30 to 40 minutes in the horse and 1 to 2 hours in the dog and cat. Complete recovery, after the recommended dose has been used, usually occurs within 2 to 3 hours in the horse; 2 to 4 hours in the dog and cat[34]; and up to 24 hours in cattle. Ruminants are the most sensitive to xylazine and require about one-tenth the dose of horses, dogs and cats[67].

2.2.2 Pharmacological effects

2.2.2.1 Respiratory function

Xylazine is reported to cause changes to respiratory function that vary from mild to severe decreases in respiratory rate, tidal volume and PaO_2; and increases in $PaCO_2$[32,91,108]. However, hypoxaemia, tachypnoea and reduced $PaCO_2$ have also been reported in both cattle and sheep. It is suggested that in these cases the hypoxaemia may initiate increased respiration, via peripheral chemoreceptor stimulation and result in a low $PaCO_2$[55,88,112].

Little information has been published regarding the effects of xylazine on respiratory function in artiodactyls. Xylazine (0.62 $\pm$ 0.3 mg/kg) given intramuscularly has been reported to result in slow, but deep respiration of approximately six breaths / minute and a mild hypoxia with elevated $PaCO_2$ levels in scimitar horned oryx. The arterial pH, however, remained unchanged[83].

Xylazine (0.6 to 1 mg/kg) administered intravenously to ponies was found not to result in statistically significant changes in arterial pH, $PaCO_2$, PaO_2, respiration rate, tidal volume or minute volume[34]. Foals given xylazine (1.1 mg/kg) intravenously, showed no changes to the arterial blood gases, but their breathing was dramatically changed. The respiration rate fell, tidal volume increased and minute volume decreased. The decrease in respiration rate occurred approximately 20 minutes after the onset of sedation. In adult horses the respiration rate fell almost immediately and tidal volume showed a similar delayed change[18].

Xylazine is reported to decrease respiratory rates in cattle and calves[108]. Several investigations have shown mild to severe decreases in PaO_2, others report both decreases and increases in $PaCO_2$. The decrease in arterial oxygenation may result in collapse and death[13,24,33,66].

In sheep, studies have shown that xylazine causes PaO_2 to decrease dramatically. This has been attributed to peripheral effects which include an increase in airway resistance, a pulmonary ventilation-perfusion mismatch in the lungs[19,81,91] or pulmonary parenchymal effects[22].

It is reported that xylazine causes a dose-dependent increase in airway pressure in halothane-anaesthetized sheep. As idazoxan, an alpha$_2$-adrenoceptor antagonist, prevents this effect and xylazine administered into the central nervous system does not increase airway pressure, it is concluded that the effect is mediated by peripherally located alpha$_2$-adrenoceptors[55]. Papazoglou *et al*[81], similarly report that xylazine induced increases in airway pressure in sheep are inhibited by the prior administration of atipamezole, a potent and highly selective alpha$_2$-adrenoceptor antagonist.

The presence of alpha$_1$-adrenoceptors in the sheep trachea can not be excluded. However, the fact that atipamezole antagonizes xylazine induced contractions of the trachea, suggests that this response is not due to alpha$_1$-adrenoceptors[82]. This is supported by the observation that xylazine induced hypoxaemia in sheep is prevented by pretreatment with the alpha$_2$-adrenoceptor antagonist idazoxan and not with the alpha$_1$-adrenoceptor antagonist prazosin[22].

The prior administration of atropine is also found to inhibit a xylazine induced increase in airway pressure in sheep[81]. However, it does not have any effect on xylazine-induced contractions of

isolated tracheal preparations. This compares to atipamezole which does prevent these xylazine induced contractions. It appears that alpha$_2$-agonists may act directly on the trachea of sheep by stimulation of peripheral adrenoreceptors. Alpha$_2$-agonists in sheep, may also act indirectly via central alpha$_2$-mediated vagal stimulation resulting in bronchoconstriction which is blocked by the prior administration of atropine *in vivo*[81,82].

Celly *et al*[22], compared the respiratory effects of xylazine, romifidine, detomidine and medetomidine in sheep. These four alpha$_2$-agonists have different alpha$_2$ / alpha$_1$ selectivity ratios, but all produced similar significant hypoxaemic responses at doses with similar sedative effects. Xylazine (0.15 mg/kg administered intravenously) caused a tachypnoea with a significant decrease in PaO_2 but no significant changes in the $PaCO_2$ were recorded, indicating that the hypoxaemia was not due to hypoventilation. The hypoxaemia was characterized by an increase in the gradient between alveolar oxygen and arterial oxygen levels. The increase in this gradient was essentially due to a decrease in the PaO_2, which indicated an increase in the degree of admixture of mixed venous blood with pulmonary end-capillary blood. Possible causes of this decrease in PaO_2 were listed as an increase in ventilation / perfusion ratios, an increase in right-to-left pulmonary shunting, a fall in cardiac output or a decreased oxygen tension in the mixed venous blood. An increase in the change in pleural pressure following the administration of the xylazine suggested that the increase in the alveolar-to-arterial oxygen gradient and the decrease in PaO_2 had a pulmonary parenchymal origin. The increase in pleural pressure indicated a change in pulmonary mechanics[22].

Further work reported by Celly *et al*[21], confirms that alpha$_2$-agonist induced hypoxaemia in sheep appears to be mediated by peripheral alpha$_2$-adrenoceptors. Furthermore, the central effects of

these drugs, such as sedation and muscle relaxation, may contribute to the hypoxaemia, but they are much less important than the peripheral effects. However, the mechanisms by which alpha$_2$-agonists induce hypoxaemia is still unclear[21].

It is also argued that if alpha$_2$-adrenoceptors are present post-synaptically in the pulmonary vascular system of sheep and that an alpha$_2$-agonist such as xylazine will activate them and cause contraction of the vascular smooth muscle, increased pulmonary vascular resistance and resulting in a ventilation-perfusion mismatch[112]. A decrease in cardiac output due to xylazine, combined with recumbency induced ventilation-perfusion mismatch, probably contributes to arterial hypoxia in ruminants[65].

In sheep, although the respiration rate usually decreases during sedation with alpha$_2$-agonists, tachypnoea may occur. Tachypnoea with open-mouth breathing or cyanosis may signal the development of pulmonary oedema[57,65].

Goats are reported to be sensitive to the effects of xylazine[100]. Intramuscular xylazine (0.22 mg/kg) is reported to cause a significant reduction in respiratory rate[13]. Male British Saanen goats given xylazine (0.01 mg/kg) intravenously developed a hypopnoea within five minutes. Respiration rates decreased from 22 ± 4 breaths/min to 17 ± 2 breaths per minute. Normal values were regained 35 minutes after the injection[97]. Kumar *et al*[69], report similar results, with significant reductions in respiration rate, pH, PaO_2, and a significant increase in $PaCO_2$ at 15 minutes after drug administration. These values returned to near pre-administration levels after two hours[69].

2.2.2.2. Cardiovascular function

The effects of xylazine on the cardiovascular system are variable. Generally, intravenous or intramuscular injections will result in an initial transitory hypertension followed by bradycardia, a fall in cardiac output and an extended period of hypotension,[9,13,67]. These variable effects are apparently related to the alpha$_1$- and alpha$_2$-adrenoceptor actions of xylazine[13]. The initial hypertension is due to an increase in peripheral resistance through vasoconstriction of splanchnic and peripheral vessels[67], which is attributed to stimulation of postsynaptic alpha$_1$- and alpha$_2$-adrenoceptors on vascular smooth muscle[33,65,104]. The subsequent bradycardia and decreased cardiac output is possibly in response to an increased baroreceptor stimulation and a reflex vagal activity due to the initial hypertension[33,65]. Alpha$_2$-agonists are believed to facilitate this baroreceptor reflex[56].

Others suggest that the central action of xylazine causes a decrease in sympathetic discharge and an increase in vagal tone. This is followed by a decrease in heart rate, cardiac contractility, cardiac output and an ensuing hypotension[9,33,65]. Xylazine reduces both central and peripheral sympathetic tone but the central action seems to predominate[98]. The decrease in sympathetic outflow in the central nervous system is believed to originate from both pre- and post-synaptic alpha$_2$-adrenoceptors in the pontomedullary region[56]. A direct depressant effect of xylazine on the contractility of the heart may result in a drop in cardiac output and an associated arterial hypotension[13].

When xylazine is given intramuscularly, the initial transient hypertension may not occur. Pre-synaptic alpha$_2$-mediated cardiovascular hypotension and decreased cardiac contractility are still

marked, and postsynaptic alpha$_2$- and alpha$_1$-mediated vasoconstriction contribute to reduced peripheral vascular perfusion[65]. Arrhythmias associated with the use of xylazine include sinoatrial block, bradycardia, first and second degree heart block, atrio-ventricular dissociation and sinus arrythmia[33].

Little has been published regarding the effects of xylazine on cardiovascular function in wild artiodactyls. Xylazine administered intramuscularly to scimitar horned oryx, results in a decrease in heart rate and the systemic arterial blood pressure during the first hour of sedation[83].

Hsu *et al*[56], report that there is an initial increase in mean arterial blood pressure lasting for at least five minutes in dogs given an intravenous injection of xylazine (1 mg/kg). This is followed by a hypotension which is significant for 45 minutes post-administration. A bradycardia occurs very rapidly following the administration of the xylazine and lasts for at least 30 minutes. Haskins *et al*[46] reports a similar result. Five minutes after intravenous administration, dogs exhibit a significant decrease in heart rate, cardiac output, a significant increase in systemic vascular resistance (by 235%), systemic blood pressure and central venous pressure. Due to a decrease in cardiac output, the marked increase in peripheral vascular resistance did not result in a proportionate increase in systemic blood pressure.

Xylazine given intravenously at 1.1 mg/kg or intramuscularly at 2.2 mg/kg to horses, depresses heart rate, cardiac output and packed cell volume for at least 45 minutes after injection[111]. Foals given xylazine intravenously show an initial rapid decrease in heart rate which gradually returns to initial values, a biphasic blood pressure response consisting of an initial increase followed by a fall[18].

Xylazine (0.04 mg/kg) administered intravenously in cattle results in a rapid decrease in heart rate followed by a gradual recovery, although initial values were not reached by 60 minutes. This is accompanied by a decrease in blood pressure, but this is not statistically significant[24]. Calves given intramuscular xylazine show cardiovascular effects similar to those seen in other species[17]. These include bradycardia, decreased stroke volume and cardiac output, and an increase in total peripheral resistance. There was no initial increase in mean arterial blood pressure. Rather initial observations four minutes after drug administration indicated a marked decrease in blood pressure. This may be due to one or more of several possible effects. Early hypertension does not appear to be part of a calf's response to xylazine, hypertension may have occurred prior to the initial observations or hypertension does not occur when xylazine is administered intramuscularly[17].

Xylazine (0.5 mg/kg) injected intravenously in sheep causes a hypertension followed by a prolonged hypotension which occurs for longer than 60 minutes, accompanied by an increase in peripheral resistance and in packed cell volume. The heart rate decreased directly after the administration of the xylazine and a bradycardia was noted for more than 60 minutes. Stroke volume and thus cardiac output also decreased. The administration of atropine did not antagonize the bradycardia[8].

An intravenous infusion of xylazine in goats was shown to result in a significant dose-related hypotension, after which the blood pressure gradually returned to the initial levels over a period of 1.5 to 3 hours depending on the dose. A bradycardia followed when incremental doses of xylazine were given but these changes only became statistically significant when higher doses (0.08 mg/kg) were administered[68]. Similarly xylazine (0.01 mg/kg) administered intravenously

to male British Saanen goats induced a bradycardia within five minutes[97]. Kumar *et al*[69], report that a dose of 0.22 mg/kg of xylazine administered intramuscularly results in a significant reduction in heart rate. The pre-administration of atropine prevented this change. There was a slight decrease in the mean arterial blood pressure accompanied by reductions in the total number of erythrocytes, haemaglobin and haematocrit, possibly due to pooling of blood in the spleen[69].

2.3 AZAPERONE

2.3.1 Introduction

Azaperone is a tranquillizer of the butyrophenone group of derivatives. It has the structural formula: 4'-fluor-4-[4-(2-pyridyl)-1-piperazinyl]-butyrophenone[14,45,64].

The effects of azaperone are produced through a central dopaminergic and peripheral adrenergic blockade[104]. Butyrophenones appear to act by mimicking the action of gamma-aminobutyric acid or by preventing the effect of glutamic acid on synaptic function in the extrapyramidal system[34]. At higher doses extrapyramidal effects including rigidity, tremor and catalepsy are often seen[32]. Azaperone produces a peripheral alpha$_1$-adrenoceptor blockade[91].

Porter *et al*[87], report that the pharmacological profile of azaperone characterizes it as a sedative and neuroleptic, with an extremely high anti-shock effect. The sedation is rapid and consistent, with a wide safety margin[26]. The state of catalepsy resulting from therapeutic doses, is characterized by the absence of voluntary movements and by a state of indifference to the environment[85]. The butyrophenones display a marked synergistic effect on the action of the

majority of the analgesic drugs and azaperone has been combined with etorphine, fentanyl and carfentanil to provide safe and effective immobilization of wild ungulates[86,87]. Harthoorn[45], suggests that the safety factor between the lowest effective dose and the lethal dose may be in excess of 1000. The degree of sedation or reduction in motor activity produced[14], appears to be proportional to the amount of drug administered[87]. The effect ranges from no sedation to moderate sedation where the animal is indifferent to visual or auditory stimuli[45]. The animals are often indifferent to the presence of people and there is an absence of fear reactions for a number of hours[86].

Porter *et al*[87] report that the first effects of the drug after intramuscular injection are usually observed within a few minutes in pigs. The drug reaches its peak effect within 15 minutes in young pigs and 30 minutes in adults and the action of the drug lasts for 2 to 4 hours. Maximum drug levels are reached in the brain, blood and liver within 30 minutes after administration and then decline rapidly[14].

The primary site of azaperone metabolism is the liver, with most of the drug being eliminated from the body tissues within 16 hours. Azaperol, the metabolite of azaperone may be present as a tissue residue[14,45]. The long-term administration of azaperone at therapeutic levels in dogs and rats has been shown to have no adverse effects on tissues, blood or urine[45].

2.3.2 Pharmacological effects

2.3.2.1 Respiratory function

Riedesel[91], indicates that ventilation is minimally affected by the butyrophenones, and the response to carbon dioxide is not altered. However, small changes in respiratory variables may be anticipated with currently recommended doses of butyrophenones[32].

It has been reported that azaperone (0.54 to 3.5 mg/kg) given intramuscularly, reduces arterial blood pressure by 16 to 30 % and reflexly stimulates respiration in pigs. Lower doses (0.03 mg/kg) given intravenously also cause an elevation in respiration and a drop in $PaCO_2$[14]. The effects of azaperone on respiration in ponies is comparable to that reported in pigs[87]. The arterial pH, $PaCO_2$ and PaO_2 remain relatively stable throughout the action of the drug in ponies given 0.4 to 0.8 mg/kg intramuscularly[34]. Azaperone given to dogs either intramuscularly (2 to 4 mg/kg) or per os (4 to 6 mg/kg) results in an increase in both rate and depth of respiration[87]. It has been suggested that azaperone has the ability to antagonize the respiratory depressant effect of morphine-like compounds[64,86]. However, a combination of droperidol (a short-acting butyrophenone) and fentanyl causes a decrease in respiratory minute volume leading to respiratory acidosis in dogs[32].

The respiratory rate in male British Saanen goats given azaperone (0.1 mg/kg) intravenously, decreased from 22 breaths/min to 16 breaths/min within 15 minutes. Baseline values were regained approximately two hours after drug administration. This decrease is attributed to the sedative effects and locomotor inactivity induced by azaperone[96].

2.3.2.2 Cardiovascular function

Azaperone does not alter myocardial contractility, but produces a slight peripheral alpha$_1$-adrenoceptor blockade, and the resultant vasodilation decreases blood pressure[91]. Juvenile elephants immobilized with either etorphine or etorphine plus azaperone administered intramuscularly show significant differences in mean arterial blood pressure. Elephants that where given etorphine only have a arterial blood pressure of 174 ± 16 mm Hg (range 137 to 212 mm Hg) compared to 120 ± 29 mm Hg (range 56 to 184 mm Hg) in those animals given etorphine and azaperone[48]. A mean arterial blood pressure of 145 ± 3 mm Hg in conscious standing elephants has been reported. A number of factors are implicated in increasing blood pressure in immobilized elephants. These include: herding and forced exercise prior to immobilization, etorphine induced hypertension and positional hypertension as the blood pressures were measured in laterally recumbent animals. The lower blood pressures measured in animals given etorphine and azaperone were attributed to the antagonistic peripheral alpha$_1$-adrenoceptor properties of azaperone[48].

Similar results are obtained in free-ranging white rhinoceroses (*Ceratotherium simum*) (estimated weights of 1600 kg) immobilized with 2 mg etorphine and 30 mg fentanyl or 3 mg etorphine and 25 mg azaperone. The mean arterial blood pressure in those animals given etorphine plus azaperone was lower when compared to the animals immobilized with etorphine and fentanyl. It is postulated that the lower blood pressure, despite the higher etorphine dose given, can be attributed to the azaperone[47].

Intramuscular azaperone in doses of 0.54 to 3.5 mg/kg, has been reported to reduce arterial blood pressure by 16% to 30% in pigs. The administration of a dose of 0.03 mg/kg intravenously, resulted in a greater drop in arterial pressure and may also cause an initial period of violent excitement, followed by good sedation[14]. It is uncertain as to whether the hypotension following either intramuscular or intravenous injection of azaperone is dose related or not[34,87]. Booth[14], suggests that the drop in arterial blood pressure is as a result of peripheral vasodilation due to alpha$_1$-adrenoceptor antagonism which prevents peripheral vasoconstriction. The skin of the pig becomes pink, ostensibly from cutaneous vasodilation[34]. Both Porter *et al*[87] and Booth[14], report that in ponies 0.4 to 0.8 mg/kg of azaperone intramuscularly resulted in similar physiological changes to those reported in pigs: lowered mean arterial pressure, moderate and transient tachycardia and moderate reductions in packed cell volumes and haemaglobin values.

Azaperone (0.1 mg/kg) administered intravenously to male British Saanen goats resulted in an initial small increase in heart rate within five minutes, followed by a progressive decline to reach baseline values two hours after azaperone administration[96].

2.4 ATIPAMEZOLE

2.4.1 Introduction

The chemical structure of atipamezole hydrochloride is (4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride)[104].

When alpha$_2$-agonists are used in immobilizing "cocktails" residual impairment of motor and mental function may remain for several hours. The development of specific alpha$_2$-adrenoceptor antagonists has been important, especially for use in free-ranging animals[65]. Atipamezole was developed specifically as an antagonist of medetomidine. It has also been used successfully in a wide range of wild animals to reverse the effects of xylazine[104].

Atipamezole is a highly potent, selective and specific antagonist of centrally and peripherally located alpha$_2$-adrenoceptors. It has an alpha$_2$ / alpha$_1$ selectivity ratio that is 200-300 times greater than yohimbine or idazoxan and is therefore a more effective antagonist. In receptor-binding studies and studies in isolated organs, atipamezole has no other significant receptor interaction[34,61,110].

The effects of xylazine are rapidly reversed by 1 mg of atipamezole for every 8 to 12 mg of xylazine used. High doses of atipamezole may result in a transient nervousness or over-alertness[104]. This may be due to unmasking of the undesirable effects of a drug that may have been used in combination with xylazine (e.g. opioids) or due to the antagonist itself[65].

2.4.2 Pharmacological effects

Atipamezole has been used to reverse xylazine-induced effects in various wild and domesticated species[5,60]. Atipamezole has been used as an antagonist in Arabian oryx (*Oryx leucoryx*) sedated with xylazine. Two thirds of the atipamezole dose was given intravenously and the rest subcutaneously. The mean reversal time, the time from recumbent to standing, was 87.1 $\pm$ 43.2 seconds. Resedation was reported to occurred in 87.5% of the animals between two and five

hours after the administration of the atipamezole[3]. Atipamezole at a dose ratio of 1 atipamezole to 10 xylazine resulted in a rapid and permanent reversal of the sedative effects of xylazine in axis deer[5]. A similar dose of atipamezole, administered intravenously or divided between intravenous or intramuscular routes reversed xylazine-induced deep sedation and immobilization in moose (*Alces alces*)[60].

A dose ratio of atipamezole to xylazine of 1:6 administered intravenously, rapidly reverses the sedative effect of xylazine in Norwegian cattle. Soon after administration the animals exhibit ear flicking, head lifting and an awareness of surroundings. All animals stand in a controlled manner without ataxia, some show temporary signs of excitement with jumping, kicking and bellowing. These animals calm down after a few minutes. At a dose ratio of atipamezole:xylazine of 1:10 rapid reversal occurs, but heavy resedation may occur as much as four hours after administration of the atipamezole. It is suggested that the ratio for antagonising xylazine in cattle should be 1:8 or even 1:4[6].

Atipamezole (0.03 mg/kg) given intravenously to calves 10 minutes after they are sedated with xylazine (ratio (w/w) of atipamezole to xylazine 1:10) significantly reduces the time from onset of xylazine induced recumbency to standing to 10.0 $\pm$ 0.7 minutes. The time from onset of lateral recumbency to standing in calves that are not administered atipamezole is greater than 60 minutes. Calves given 0.03 mg/kg of atipamezole, do not relapse into deep sedation as occurs when only 0.003 mg/kg is administered[105]. These results compare with those reported by Arnemo *et al* [7]. The recommended atipamezole : xylazine dose ratios (w/w) for reversal of xylazine-induced sedation in dairy calves are 1:3.3 and 1:4 intramuscularly or 1:5 and 1:8 intravenously. Animals given higher doses of atipamezole exhibit signs of excitement and over

alertness, with jumping, kicking and vocalization. Incomplete reversal and resedation occurs at lower doses of atipamezole[7].

2.5 DIPRENORPHINE

2.5.1 Introduction

Diprenorphine is structurally similar to etorphine[72] and is chemically N-(cyclopropylmethyl)-6,7,8,14-endo-tetrahydro-7-91-hydroxyl-1-methylethy)-6,14-endo-ethano-nororipavine hydrochloride[12].

Diprenorphine is classified as a mixed antagonist, retaining some agonistic activity. As it's action is much closer to that of an antagonist it is routinely used as a reversing agent for etorphine[72,104].

2.5.2 Pharmacological effects

Alford *et al*[2], indicate that diprenorphine at twice the dose of etorphine, is capable of reversing all the opioid's effects in wild animals. However, reported effective ratios of diprenorphine to etorphine in various wild animal species vary from 1:2 to 4:1[27,28,120]. 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 as compared to a few seconds to four minutes if given intravenously[2].

CHAPTER 3

MATERIALS AND METHODS

3.1 STUDY ANIMALS

3.1.1 Introduction

Eight non-pregnant female Boer goats of a similar age and body mass were used in the study. Six were required for the research trials and two were kept as replacement animals to be used in the event of any drop-out. Each goat was identified by a numbered ear tag. The goats were housed in a fenced enclosure 20 m x 10 m and had access to covered night quarters. The enclosure was bare earth and contained no natural vegetation. Baled lucern and antelope cubes (Epol, Premier Food Industries Limited, Johannesburg, SA) were fed daily. Fresh drinking water was available *ad libitum*.

3.1.2 Carotid artery translocation

The left carotid of each goat was relocated surgically to a subcutaneous position in the neck to facilitate the collection of arterial blood samples and the recording of arterial blood pressures.

Food and water were removed for 17 to 20 hours prior to the surgery. Anaesthesia was induced with a 1:1 combination of tiletamine hydrochloride and zolazepam (Zoletil, Logos Agvet, Halfway House S.A.), given intravenously. A dose of 2.5 to 3.0 mg/kg of the drug combination

was used. Surgical anaesthesia was maintained during the procedure using halothane (Fluothane, Zeneca, Woodmead S.A.) administered with a face mask.

The surgical technique used was a modification of that described by Butler[16]. The animal was placed in right lateral recumbency with its head extended and it's forelimbs pulled backwards. The surgical site was prepared and draped in a recognized manner. The left carotid was palpated and a 12 cm skin incision was made along its length midway between the angle of the jaw and the thoracic inlet. Approximately 8 cm of the carotid artery was exposed from below the sternocephalicus and omohyoideus muscles by blunt dissection. Once the artery had been separated from the fibrous sheath containing the vagus and sympathetic nerves, it was brought to the surface, held in place by suturing the subcutaneous tissue beneath it and the skin was closed using nylon sutures. A long-acting penicillin (Peni LA Phenix, Logos Agvet, Halfway House S.A.) was administered intramuscularly. Each animal was allowed to recover in a separate enclosure before it was returned to the herd. The surgical site was examined daily to ensure that there was no secondary infection and the sutures were removed at ten days.

3.1.3 Clinical examination

Each goat was examined clinically and blood samples were collected for haematology and blood chemistry examination. Faecal flotations were done on fresh samples collected randomly from the enclosure in which the goats were housed. Each goat was treated at the time of the clinical examination with 1 ml of Ivermectin 1% m/v (Ivomec injectable, Logos Agvet, Halfway House, S.A.), administered subcutaneously.

3.2 TRAINING OF THE GOATS

3.2.1 Introduction

To prevent the goats from becoming unduly distressed or excited during the trials they were habituated to standing on a low research table while restrained by their horns; being handled; the 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.

3.2.2 Training

Four training enclosures with dimensions similar to those of the research table (50 cm x 82 cm x 113 cm) were used for the habituation process. These enclosures had wooden slatted floors raised 30 cm off the ground , wire mesh walls and roof, and a wooden sliding door. The goats were coaxed into the cages using lucern and antelope cubes. The time spent by each goat in an enclosure was gradually increased from ten minutes to two hours daily. They were also handled for progressively longer times each day. In the final stages of the training process each goat underwent the sequence of procedures in preparation for a trial. This was done on the research table. The training period lasted for eight weeks.

3.2.3 Research table

The research table was constructed of a solid wooden floor which stood 60 cm above the ground. The sides consisted of four rectangular frames. The two side frames had horizontal metal strips placed 8 and 16 cm from the bottom edge and two placed vertically 20 and 26 cm from the back edge. This allowed the operator easy access to the animals. It also prevented the goats from falling off the table, especially when immobilized. An overhead bar was fixed down the centre and above the table. The goat's horns were tied to this bar to restrain the animals and support their heads in an upright position when immobilized.

3.3 CLINICAL TRIALS

3.3.1 Introduction

The experiment structure was expressed in the form of an open, randomized, single dose, three-way crossover design in the form of a Randomized Latin Square (Table 3.1). There was a washout period between treatments of two weeks. Six goats, the calmest when standing on the research table, were selected for the final trials. Two goats, numbers 424 and 410, were kept as replacement animals and housed with the experimental group. Both, the order in which the goats were selected and in which they received the three treatments, was randomized. Goat 422, died while undergoing treatment II and was replaced by goat 424.

Table 3.1 The order of treatment allocation to the goats.

	Goats					
Eartag Number	**421**	**417**	**422**	**409**	**420**	**415**
Treatment	**II**	**III**	**II**	**III**	**III**	**I**
	I	**II**	**III**	**I**	**II**	**III**
	III	**I**	**I**	**II**	**I**	**II**

Three treatments (I - III), consisting of an immobilizing drugs and antagonists were used (Table 3.2).

Table 3.2 The three treatments administered to the goats

Treatment	Immobilizing Drugs	Antagonists
I	**Etorphine 30 µg/kg im**	**Diprenorphine 3 mg / 1mg Etorphine iv**
II	**Etorphine 30 µg/kg im** **Xylazine 0.22 mg/kg im**	**Diprenorphine 3 mg / 1 mg Etorphine iv** **Atipamezole 1 mg / 8 mg Xylazine iv**
III	**Etorphine 30 µg/kg im** **Azaperone 0.50 mg/kg im**	**Diprenorphine 3 mg / 1 mg Etorphine iv** **No antagonist**

The drugs used were: etorphine hydrochloride (M99, Logos Agvet, Halfway House, S.A.), xylazine hydrochloride (Chanazine, Centaur (Sanvet), Silverton, S.A.), azaperone (Azaperone, Kyron Laboratories, Benrose, S.A.), diprenorphine hydrochloride (M5050, Logos Agvet, Halfway House, S.A.) and atipamezole hydrochloride (Antisedan, Ciba-Giegy A.H., Isando, S.A.). The total volume of the immobilizing drugs was standardized at 2 ml using sterile water. The drug antagonists were drawn up separately into 1 ml syringes.

All the trials were conducted in the morning. One trial was done per day. Each goat was rested for a period of at least two weeks between different treatments.

3.3.2 Housing of goats

Two weeks prior to the start of the final trials the goats were moved to a medical research facility. They were housed in night quarters with an adjacent grassed exercise area. The night quarters were ventilated and kept at a constant temperature of 18 ^{0}C. The goats were kept indoors overnight and given access to the grassed area during the day. Food was removed 17 hours and water 2 hours prior to the start of each trial.

3.3.3 Preparation prior to each trial

3.3.3.1 Research room

The trials were conducted in a 3 m x 6 m room which was ventilated, kept at a constant temperature and illuminated by flourescent lights.

3.3.3.2 Recording of data

All data collected was recorded on a "Research Data" sheet. This included the identification number and mass of the goat, and the date. The dose rate, total dose, concentration and volume

required for each drug being used in the trial were calculated and recorded, as were the time and collection of all samples and data.

3.3.3.3 Initial preparation of the goat

The goat was weighed. An area of hair 10 cm^2 was shaved on the lateral surface of each leg, the forearm above the carpii and the hindleg above the hocks. The center of each of these areas was marked and 2 ml of 2% lignocaine hydrochloride (Lignocaine 2%, Centaur (Sanvet), Silverton, S.A.) was injected subcutaneously at this site. Sixteen gauge steel hypodermic needles, with attachments for the ECG leads, were inserted subcutaneously at the anaesthetised site and fixed in place with adhesive tape. The goat's neck was shaved from immediately below the mandible to the level of the thoracic inlet. A long-acting penicillin (Peni LA Phenix, Logos Agvet, Halfway House S.A.) was administered intramuscularly.

3.4.3.4 Preparation of the monitoring equipment

The vital signs monitor (DINAMAP™ PLUS Vital Signs Monitor Model 8720 plus Printer Module, CRITIKON, Johnson & Johnson, Halfway House, SA) was checked and standardized each day prior to being attached to the animal.

Two pressure transducers (Deltran II, Gabler Medical, Randburg, S.A.) were connected via a bifurcated fluid administration set to a one liter bag of sodium chloride 0.9% solution (Sabax, Adcock Ingram Critical Care LTD, Johannesburg, SA) to which 5000 IU of heparin sodium

(Heparin Novo, Novo Nordisk, Sandton, S.A.) had been added. The bag was maintained at a pressure of between 150 to 300 mm Hg using a disposable pressure infusor (Infusable, Gabler Medical, Randburg, S.A.). The pressure transducers could be flushed manually and automatically. Each pressure transducer was attached to a pressure line, to which was connected a 3-way-stop-cock. During the preparation procedure the transducers and pressure lines were flushed with heparinized saline. The calibration of the pressure transducers were checked against a mercury column using a sphygmomanometer. The pressure transducers were positioned at the approximate height of the heart of the goat standing on the research table. The systolic, diastolic and mean blood pressures and the wave form measured by each transducer was displayed and recorded on the vital signs monitor. The heart rate, determined from the arterial pulse was also displayed.

The ECG monitor was checked and standardized each day prior to being attached to the animal. A paper speed of 50 mm / s and a sensitivity of 40 mm / mV were selected. The machine was set to print the waveforms of leads I, II and III.

The cardiac output computer (Life Scope 12, Selwyn Sher, Electromedical, Johannesburg, S.A.) had a control console which was attached to the head end of the research table. This console was used to reset the computer prior to each cardiac output determination. The computer was checked and standardized each day.

3.3.3.5 Final preparation of the goat

Once the goat was standing on the research table, it was fastened to the overhead bar by a nylon rope tied around the base of its horns. The animal was blindfolded, it's ears were plugged with cotton wool and attached to the horns with adhesive tape. The ECG leads were attached. The thermometer probe was placed 10 cm into the rectum and fastened to the base of the tail with adhesive tape. The rectal body temperature was displayed and recorded by the vital signs monitor.

An arterial catheter (20G Radial Artery Catheterization Set, Arrow Africa, Sandton S.A.) was inserted into the translocated carotid artery and the percutaneous sheath introducer for the thermodilution catheter (Percutaneous Sheath Introducer Set with Side Port/Hemostasis Valve, Arrow Africa, Sandton S.A.) was inserted into the right jugular vein under aseptic conditions. Local anaesthetic (Lignocaine injection 2%, Bayer Animal Health, Isando S.A.) was placed subcutaneously at the insertion points and the skin incised to facilitate the placement of the catheter and the introducer. Both were sutured to the skin to keep them in place.

The position of the trachea was palpated and at the thoracic inlet, the overlying skin was marked with a black permanent marker on the midline over the trachea. This site was infiltrated with 3 ml of 2% lignocaine at this position. During the trial, a 1.2 x 38 mm hypodermic needle was inserted into the trachea at this site for the collection of end of expiration air samples.

A thermodilution catheter (7 French gauge, Infusion port five lumen thermodilution catheter, Arrow Africa, Sandton S.A.) was used in each trial to determine cardiac output, collect mixed venous blood samples from the pulmonary artery and for the administration of the immobilizing drug antagonists. Each catheter was used for a maximum of two trials and then replaced.

Prior to the insertion of the thermodilution catheter into the jugular vein, the catheter's thermistor was connected to the cardiac output computer and the pulmonary artery distal lumen was connected to a pressure transducer and the vital signs monitor. The pressure line to the pulmonary artery distal lumen was flushed with heparinized saline and cleared of all air bubbles. The pressure transducer were zeroed at atmospheric pressure. The catheter was then inserted via the percutaneous sheath introducer into the jugular vein and passed down through the right ventricle and into the pulmonary artery. Changes in the systolic, diastolic and mean blood pressures and variations in the waveform trace were used to determine the position of the catheter as it was advanced. 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. Cardiac function during the insertion of the thermodilution catheter and during the trial was monitored via the ECG waveform.

When the tip of the thermodilution catheter reached the right ventricle, the height of the attached pressure transducer was raised or lowered until the diastolic pressure value was zero. The height of the pressure transducer was marked with a permanent black marker on the skin of the goat, in front of the foreleg. This mark was used as the reference height to which the pressure transducer was lowered or raised during the trial as the goat lay down or stood up.

3.3.4 Collection of data and samples

3.3.4.1 Introduction

Once a goat had been prepared it was left to stand quietly for 10 minutes before the start of the trial. During the trial samples and data were collected at ten minute intervals, starting at 25 minutes prior to the injection of the immobilizing drugs. These included: systemic mean arterial blood pressure, heart rate, cardiac output, mixed venous and arterial blood samples, expired and end-expired (alveolar) air, respiratory rate and body temperature. This data was collected on three occasions prior to drug administration.

The immobilizing drugs were administered by deep intramuscular injection at time 0 minutes. A standard injection site 5 cm from the *Trochanter major* on an imaginary line towards the *Tuber ischiadicum* on the right of the animal was used. The diprenorphine was administered intravenously at 40 minutes post drug administration (PDA), i.e., after administration of the immobilizing drugs. Atipamezole was administered intravenously at 70 minutes PDA if xylazine was included as one of the immobilizing drugs. All trials ended at 95 minutes PDA, except when azaperone was included in the immobilizing drugs. In this case the trials ended at 75 minutes PDA.

3.3.4.2 Thermodilution cardiac output determinations

A 5% glucose saline solution (Sabax, Adcock Ingram Critical Care LTD, Johannesburg, SA) was used as the injectate for the thermodilution cardiac output determinations. Twenty 10 ml syringes were placed in a holding rack in an ice bath. Each syringe was filled with exactly 5 ml of injectate. The ice bath temperature was monitored during the trial using the temperature probe of the cardiac output computer and was maintained at less than 0.5 ^{0}C by the addition of ice when required.

A series of at least five measurements were performed for each cardiac output determination. The injectate lumen of the thermodilution catheter was initially flushed with 5 ml of injectate, to cool it down. The measurements were performed in rapid succession, one after the other. For each measurement; the cardiac output computer was manually reset, a syringe of injectate withdrawn from the ice bath and attached to the injectate lumen and the injectate was injected as rapidly as possible. This procedure was performed by the same person for the duration of the trials.

3.3.4.3 Collection of blood samples

Arterial and venous blood samples were collected for blood gas analysis at 10 minute intervals during each trial. Each syringe was prepared by filling the "dead space" of the syringe with heparin sodium, 5000 IU/ml. The syringe was then sealed with a tip cap (Medical distributors

Ltd, Halfway House S.A.). Each syringe was labelled to indicate whether it contained an arterial or a venous blood sample.

The arterial blood sample was collected from the intra-arterial catheter in the carotid artery. The venous blood sample was collected from the pulmonary artery using the distal lumen of the thermodilution catheter. All samples were collected anaerobically, placed in an ice-bath and processed within 10 minutes. Both the arterial and venous blood samples were analysed in a haemoximeter (OSM3, Medical Distributors Ltd., Halfway House, S.A.) and a bloodgas apparatus (ABL 500, Medical Distributors Ltd., Halfway House S.A.). The haemoximeter was calibrated for analyzing blood collected from goats.

3.3.4.4 Expired air samples

The expired air was collected using a face mask which fitted with an air tight seal around the base of the nose of the goat. The mask was tied in place behind the animals ears using bandage strips. A valve with inspiration and expiration ports (Ambu Patient valve for a Mark III resuscitator, Trigate Pty Ltd, Blairgowrie, S.A.) was fitted into the open end of the mask. The expired air was collected in a 200 gm meteorological balloon (Totex Meteorological balloon, C.W. Price and Company, Sandton, S.A.) connected to the expiration port. The collection occurred over one or three minutes. During the collection of the expired air the respiration rate was also counted. Immediately following the collection of the expired air, the balloon was sealed and a 50 ml air sample was collected from the neck of the balloon into a glass syringe. This sample was processed in the bloodgas apparatus. The volume of expired air remaining in the balloon was measured in a spirometer. The temperature of the spirometer was recorded.

3.3.4.5 End expired air samples

End expired air samples were collected into a glass syringe using a needle inserted through the skin and into the trachea at the thoracic inlet. The samples were immediately analyzed in the bloodgas apparatus.

3.3.4.6 Room air samples and temperature

The gas content of the air in the room was determined and the temperature recorded on three occasions during the trial.

3.4 CALCULATION OF DERIVED VARIABLES

3.4.1 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 as follows:

$$\dot{V}_{E\,BTPS} = \dot{V}_{E\,ATPS}\left[\frac{273 + T_B}{273 + T_S}\right]\left[\frac{P_b - P_{H_2O_S}}{P_b - P_{H_2O_B}}\right] \qquad (1)^{117}$$

$\dot{V}_E$	Respiratory minute volume
T	Temperature
P_b	Barometric pressure
P_{H_2O}	Vapour pressure of water.
B	Body
S	Spirometer

The P_{H_2O} was read from tables for the temperature in degrees celsius , to the nearest 0.2 °C [4].

All respiratory volumes measured at ATPS , were reported and discussed at BTPS.

3.4.2 Tidal volume$_{(BTPS)}$

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

$$V_{T_{BTPS}} = \frac{\dot{V}_{E\,BTPS}}{R} \qquad (2)^{38}$$

V_T	Tidal volume
R	Respiratory rate

3.4.3 Alveolar minute ventilation$_{(BTPS)}$

$$\frac{V_D}{V_T} = \frac{PaCO_2 - P_ECO_2}{PaCO_2} \qquad (3)^{119}$$

V_D	Dead space
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
P_ECO_2	Partial pressure of carbon dioxide in expired air

Solving the equation for V_D

$$V_D = V_T\left[\frac{PaCO_2 - P_ECO_2}{PaCO_2}\right] \qquad (4)$$

Alveolar ventilation is equivalent to the tidal volume minus the dead space ventilation, i.e.

$$V_A = V_T - V_D \qquad (5)^{119}$$

V_A	Alveolar ventilation

Substituting $V_T\left[\frac{PaCO_2 - P_ECO_2}{PaCO_2}\right]$ for V_D

$$V_A = V_T\left[1 - \left[\frac{PaCO_2 - PECO_2}{PaCO_2}\right]\right] \quad (6)$$

As V_A is measured per unit time (i.e. $\dot{V}_A$), V_T was multiplied by the respiratory frequency per unit time and is therefore $\dot{V}_E$. All volumes were measured at ATPS and converted to BTPS.

$$\dot{V}_{A\,BTPS} = \dot{V}_{E\,BTPS}\left[1 - \left[\frac{PaCO_2 - PECO_2}{PaCO_2}\right]\right] \quad (7)$$

3.4.4 Physiologic shunt fraction

The oxygen saturation of the systemic arterial blood was calculated using the algorithm reported by Watney[113]. No algorithm was available for goats. The algorithm indicated for sheep was found to be unsuitable for goats, as negative physiologic shunt fractions resulted. Rather the algorithm and constants indicated for cattle were used. The oxygen tension used was the PAO_2. It was accepted that the PAO_2 was equal to the PaO_2 of the end capillary blood, as the difference between them is normally immeasurably small[114]. This would also give an "ideal oxygen saturation" and allow the calculation of the " ideal oxygen concentration of the end capillary blood".

$$\ln\left[\frac{S}{1-S}\right] = B_0 + B_1\left[\ln PAO_2\right]^{1.78} \quad (8)^{113}$$

S	Arterial blood oxygen saturation
B_0	Constant = -5.756
B_1	Constant = 0.709
P_AO_2	Partial pressure of oxygen in alveolar air

Substituting for S, the "ideal oxygen concentration" of the end capillary blood was calculated.

$$CiO_2 = \left[[Hb]_a \times S \times 1.34\right] + \left[P_AO_2 \times 0.003\right] \quad (9)^{42,116}$$

CiO_2	Ideal oxygen concentration of end capillary blood
$[Hb]_a$	Arterial haemoglobin concentration

Substituting for CiO_2 the physiologic shunt fraction was calculated

$$\frac{\dot{Q}PS}{\dot{Q}} = \frac{CiO_2 - CaO_2}{CiO_2 - CvO_2} \quad (10)^{116}$$

$\dot{Q}PS$	Physiologic shunt blood flow per minute

The physiologic shunt fraction was expressed as a percentage.

3.4.5 Physiologic dead space ventilation fraction

$$\frac{V_{D_{PHYS}}}{V_T} = \frac{PaCO_2 - P_ECO_2}{PaCO_2} \qquad (11)^{116}$$

$V_{D_{PHYS}}$ Physiologic dead space

The physiologic dead space ventilation fraction was expressed as a percentage

3.4.6 Total peripheral resistance

Total peripheral resistance is calculated from the change in pressure (i.e., between the mean arterial pressure and the right atrial pressure) divided by the blood flow (i.e., cardiac output).

$$TPR = \frac{MAP - RAP}{\dot{Q}} \qquad (12)^{37}$$

As the normal right atrial pressure is approximately zero:

$$TPR = \frac{MAP}{\dot{Q}} \qquad (13)^{41}$$

TPR	Total peripheral resistance
MAP	Systemic mean arterial blood pressure
RAP	Right atrial pressure
$\dot{\mathbf{Q}}$	Cardiac output

3.4.7 Stoke volume

$$\mathbf{SV} = \frac{\dot{\mathbf{Q}}}{\mathbf{HR}} \qquad (14)^{30}$$

SV	Stroke volume
HR	Heart rate per minute

3.4.8 Oxygen consumption index

The oxygen consumed by the body was considered to be equivalent to the rate of oxygen uptake by the blood, as it passed through the lungs, per minute per kilogram body weight.

$$\dot{\mathbf{V}}\,\mathbf{O_2} = \dot{\mathbf{Q}}[\mathbf{CaO_2} - \mathbf{CvO_2}] \qquad (15)^{30}$$

$\dot{V}O_2$	Oxygen consumption
CaO_2	Concentration of oxygen in arterial blood
CvO_2	Concentration of oxygen in mixed venous blood

This was divided by the body weight of the goat to give an oxygen consumption index[50].

$$OCI = \frac{\dot{Q}[CaO_2 - CvO_2]}{BW} \quad (16)$$

OCI	Oxygen consumption index
BW	Body weight

3.5 STATISTICAL ANALYSIS OF DATA

Statistical analysis of the collated data was performed using the Statistical Analysis System (SAS®[a]). As the data was unbalanced due to some missing observations, statistical analysis was done using General Linear Models (GLM).

[a]The SAS system is an integrated system of software providing complete control over data access, management, analysis, and presentation, and is marketed by SAS Institute SA (Pty) Ltd, 93 Central Street, PO Box 2837, Houghton, 2041, RSA

3.5.1 General linear model

Dependent variable = Class variable + Covariable 1

Dependent variable

Two models and therefore, two different dependent variables were utilized:

a) Variables determined for each time interval for the physiological variables examined (e.g. PaO_2, alveolar minute ventilation, cardiac output, etc.), for each drug combination, i.e. within the drug. These included variables between the mean baseline value at rest (MBVR) and variables measured at any subsequent time interval for each drug.

b) Variables determined at the same time intervals for each physiological variable but resulting from different treatments, i.e. across the drugs.

Class variable

The class variable had three levels, that is etorphine, etorphine / xylazine and etorphine / azaperone.

Covariable 1

The covariable 1, was the mean of the three values measured at -15, -10 and -5 minutes when the goats were standing at rest, ie. MBVR. In developing the GLM the square of MBVR

(SQMBVR) was initially included as a second covariable to ensure 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 models.

The GLM did an initial F-test to determine if 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 and between treatments within time intervals.

CHAPTER 4

RESPIRATORY FUNCTION

4.1 RESULTS

Refer to Appendix A for a summary of statistical analyses.

In all trials, the goats became immobilized within five minutes of drug administration, irrespective of the immobilizing drugs used. Each goat was considered to be immobilized once it lay down in sternal recumbency and no longer responded to the application of artery forceps across a coronary band. Salivation was seen in all animals.

The administration of either diprenorphine or atipamezole resulted in an increase in activity in the goats. This included: vocalization; movement of head and limbs; some animals would attempt to stand; and urination or defaecation would frequently occur. This period lasted for a few minutes and then the goat returned to sternal recumbency and to a state resembling moderate sedation in which the animal remained quietly in sternal recumbency unless touched or disturbed by a loud noise. Once the blindfold and earplugs were removed the goat became aware of and responded to their surroundings.

4.1.1 Etorphine

4.1.1.1 Immobilization (0 to 40 min)

The PaO_2 decreased significantly and reached a minimum value five minutes after the administration of etorphine. It then gradually increased until the diprenorphine was given (Fig. 4.1). These changes to the PaO_2, were mirrored by a rapid and significant rise in the $PaCO_2$ followed by a gradual decrease (Fig. 4.2). At 35 minutes PDA, the $PaCO_2$ had returned to its baseline value. The arterial pH declined rapidly during the initial five minutes, and then underwent a gradual and significant increase during the remaining period of immobilization (Fig. 4.3).

Respiratory minute volume and alveolar minute ventilation decreased significantly and both reached minimum values 15 minutes PDA (Fig. 4.4 & 4.7). The decrease in respiratory minute volume was due to significant changes in respiratory rate rather than in tidal volume (Fig. 4.5 & 4.6). The respiratory minute volume and alveolar minute ventilation subsequently increased significantly over time until the diprenorphine was administered.

The physiologic shunt fraction did not change significantly during the period of immobilization (Fig. 4.8). The percentage physiologic dead space ventilation decreased significantly within five minutes of drug administration and did not change thereafter until the diprenorphine was administered (Fig. 4.9).

4.1.1.2 Recovery (40 to 95 min)

The administration of diprenorphine resulted in a rapid return of the PaO_2, $PaCO_2$ and arterial pH values to their respective baseline values (Fig. 4.1, 4.2 & 4.3). There was an immediate, although temporary rise in the respiratory minute volume, due to non-significant increases in both respiration rate and tidal volume (Fig. 4.4, 4.5 & 4.6). The alveolar minute ventilation returned its baseline value within five minutes and subsequently did not change significantly. (Fig. 4.7).

The physiologic 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. 4.9).

4.1.2 Etorphine / xylazine

4.1.2.1 Immobilization (0 to 40 min)

A highly significant and rapid change in the PaO_2 and $PaCO_2$ followed the injection of etorphine / xylazine. Within five minutes, the PaO_2 had dropped to a minimum value and the $PaCO_2$ risen sharply. Subsequently, neither of these partial pressures changed significantly (Fig. 4.1 & 4.2). The arterial pH decreased to a minimum value within five minutes and remained significantly depressed until the first antidote was administered (Fig 4.3).

The respiratory minute volume and alveolar minute ventilation, decreased significantly within five minutes of the drug administration and then did not undergo further significant changes (Fig. 4.4 & 4.7).

The physiologic shunt fraction increased significantly to a maximum value at five minutes PDA (Fig. 4.8). The percentage physiologic dead space ventilation rose more slowly, reaching a maximum value within 15 minutes (Fig.4.9). Both, were still significantly elevated prior to the administration of the diprenorphine.

4.1.2.2 Recovery (40 to 95 min)

In the five minutes following the administration of diprenorphine, the PaO_2, $PaCO_2$ and arterial pH partially returned to their baseline values (Fig. 4.1, 4.2 & 4.3). Thereafter these gains were lost and it was only after the administration of atipamezole that they returned to their respective baseline values.

The changes in respiratory minute volume and alveolar minute ventilation following the administration of diprenorphine and then atipamezole were similar to those that occurred with the arterial blood gases (Fig. 4.4 & 4.7). The diprenorphine resulted in increases in both the respiratory minute volume and the alveolar minute volume within five minutes of its administration. These two respiratory volumes subsequently decreased and only returned to their baseline values after the administration of the atipamezole. The changes in respiratory minute volume were due to adjustments in both respiratory rate and tidal volume (Fig. 4.5 & 4.6).

Diprenorphine resulted in a decrease in the percentage physiologic shunt towards the baseline value for 10 minutes. This was followed by an increase and only after the administration of atipamezole did it return to its baseline value (Fig. 4.8). The injection of diprenorphine had no significant effect on the percentage physiologic dead space ventilation, whereas atipamezole resulted in a highly significant reduction, to below the baseline value (Fig. 4.9).

4.1.3 Etorphine / azaperone

4.1.3.1 Immobilization (0 to 40 min)

The PaO_2 decreased significantly to a minimum value and the $PaCO_2$ rose significantly within five minutes of injecting etorphine / azaperone (Fig. 4.1 & 4.2). These partial pressures did not change significantly thereafter. The arterial pH decreased significantly, reaching a minimum value at 15 minutes PDA, followed by a gradual and significant increase over time (Fig. 4.3).

The respiratory minute volume and alveolar minute ventilation both decreased significantly within five minutes of administering the immobilizing drugs, and then subsequently did not change significantly (Fig. 4.4 & 4.7). The changes in the respiratory minute volume were due to significant decreases in both respiratory rate and tidal volume (Fig. 4.5 & 4.6).

The percentage physiologic shunt increased significantly following the injection of the immobilizing drugs and remained elevated until the administration of the diprenorphine (Fig.

4.8). The percentage physiologic dead space ventilation underwent a significant and progressive decrease during the same time period (Fig. 4.9).

4.1.3.2 Recovery (40 to 75 min)

The PaO_2 and the $PaCO_2$ both returned to their respective baseline values following the administration of the diprenorphine (Fig. 4.1 & 4.2). There was no significant change to the arterial pH (Fig. 4.3). There was an initial rapid elevation in both the respiratory minute volume and the alveolar minute ventilation to above their respective baseline values (Fig. 4.4 & 4.7) as a result of significant changes in both respiratory rate and tidal volume (Fig. 4.5 & 4.6). The volumes once again decreased over time.

The percentage physiologic shunt decreased within five minutes of administering the diprenorphine, returning to its baseline value (Fig. 4.8). There was no change to the percentage physiological dead space ventilation (Fig. 4.9).

4.1.4 Comparisons between the three treatments

4.1.4.1 Induction, Immobilization and recovery (- 5 min to 45 min)

Arterial PaO_2

Each of the immobilizing drug treatments resulted in significant decreases in the PaO_2 from 5 to 35 minutes post-drug administration (Fig. 4.1). The greatest fall took place after etorphine / xylazine followed by etorphine / azaperone and lastly etorphine administered on its own. Statistically, the decreased PaO_2 values due to etorphine or etorphine / azaperone were not

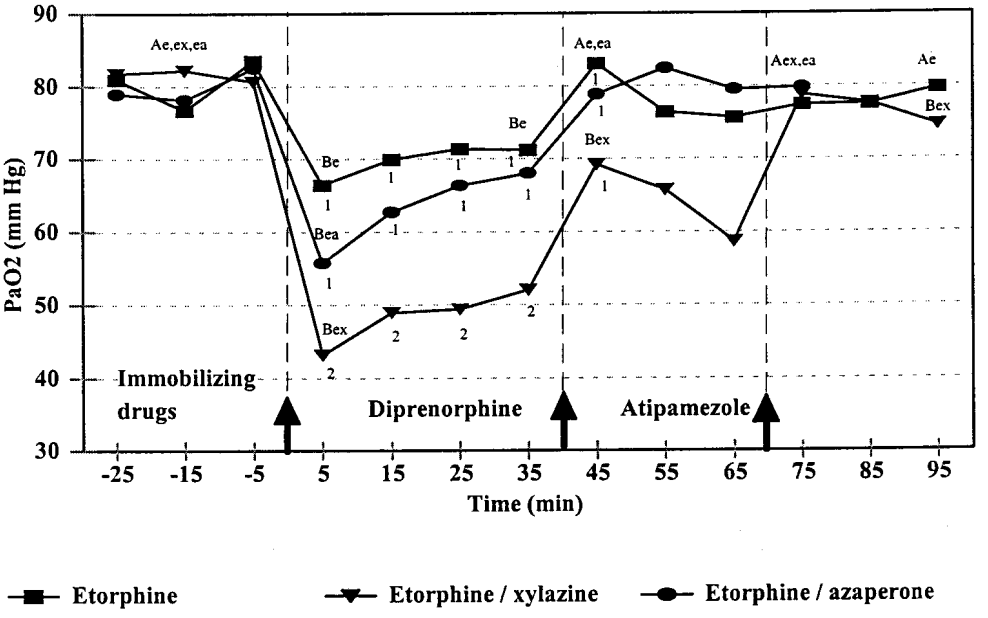

Fig. 4.1 Mean arterial PaO_2 in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

significantly different from each other but both were significantly different from those due to etorphine / xylazine.

The administration of diprenorphine resulted in the PaO_2 returning to baseline values in the goats when they were immobilized with etorphine or etorphine / azaperone but not when they had receiving etorphine / xylazine.

Arterial $PaCO_2$

All of the treatments resulted in rapid increases in the $PaCO_2$. The greatest rise was measured after the administration of etorphine / xylazine, followed by etorphine / azaperone and then etorphine only (Fig 4.2). The values measured in animals immobilized with etorphine or

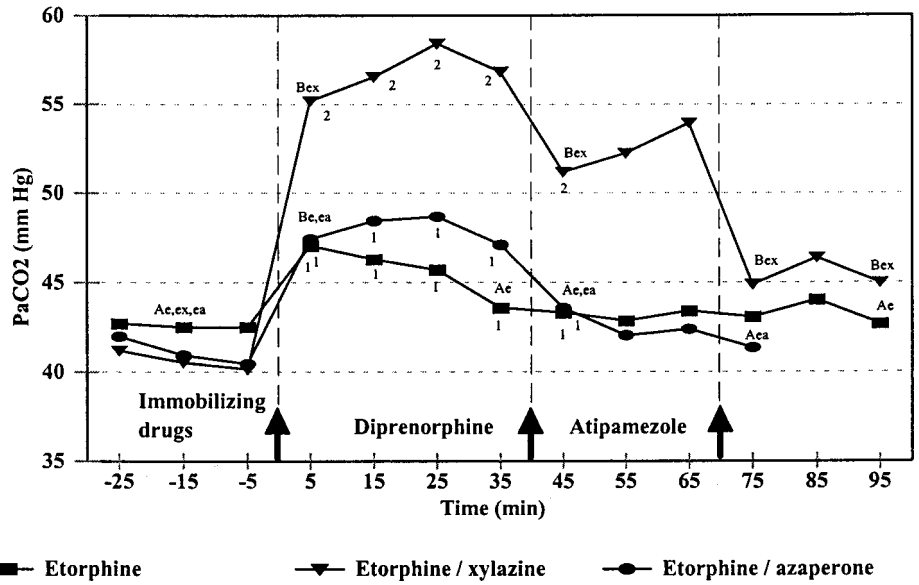

Fig. 4.2 Mean arterial $PaCO_2$ in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

etorphine / azaperone were not significantly different from each other, but they were both significantly lower than those resulting from the administration of etorphine / xylazine.

The injection of diprenorphine was followed by a return of the $PaCO_2$ to baseline values when the goats had been immobilized with etorphine or etorphine / azaperone but this did not occur when they had received etorphine / xylazine. In these animals the $PaCO_2$ remained significantly elevated.

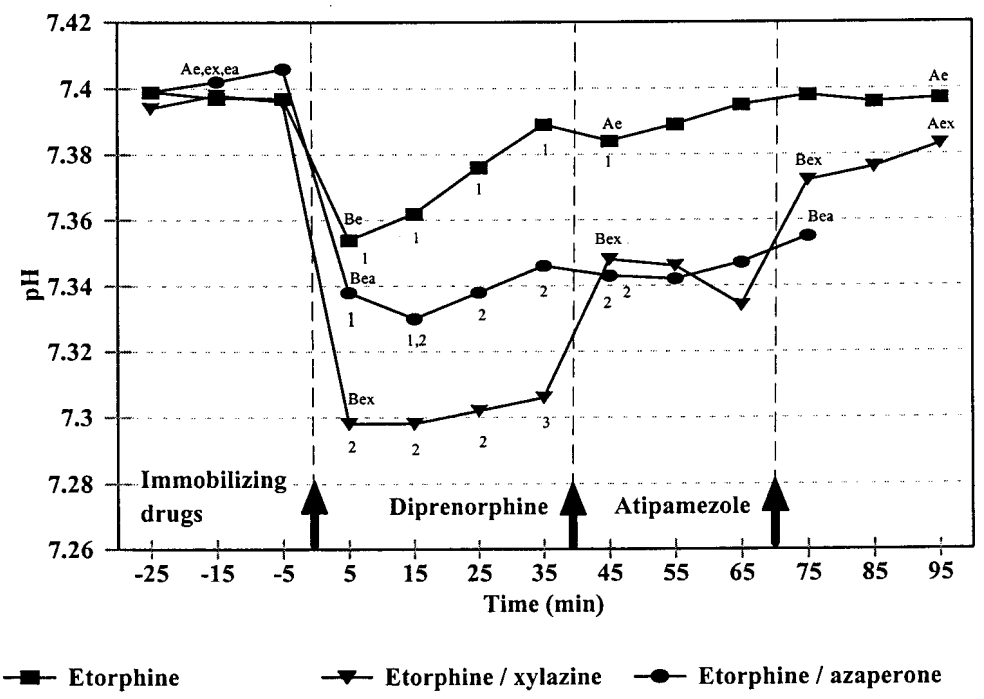

Fig. 4.3 Mean arterial pH in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Arterial pH

The arterial pH decreased significantly with the administration of each of the three treatments (Fig. 4.3). The pH after etorphine was significantly higher than the pH resulting from etorphine / xylazine, and it became significantly greater than the pH after etorphine / azaperone towards the latter half of the period of immobilization. The pH measured after immobilization with etorphine / azaperone was significantly more alkaline than the pH resulting from the administration of etorphine / xylazine at 5 and 35 minutes PDA.

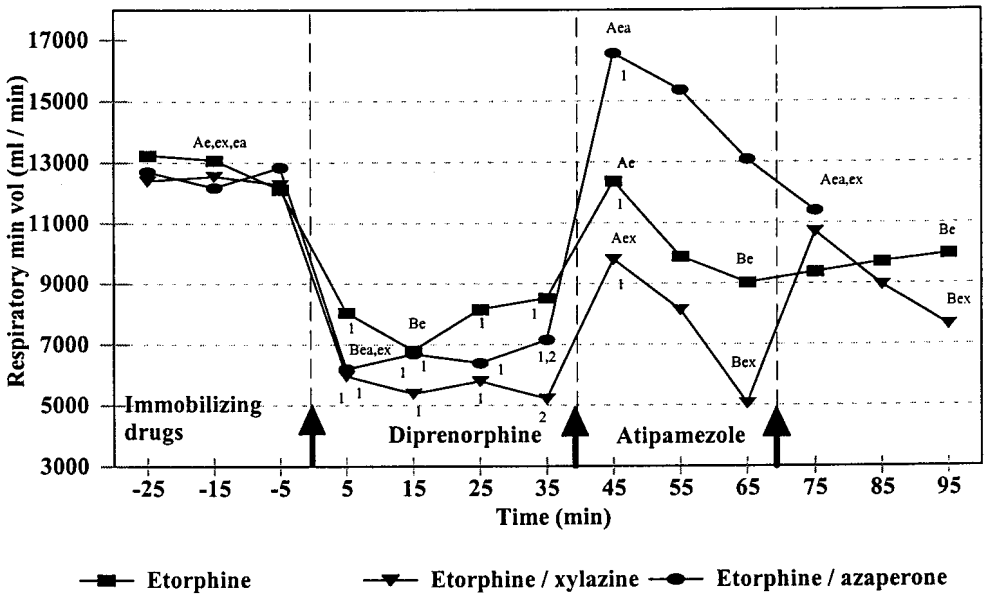

Fig. 4.4 Mean respiratory minute volume in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

The administration of diprenorphine resulted in the arterial pH returning to the baseline value when the goats had been injected with etorphine, no change occurred when they had received etorphine / azaperone and a partial increase toward the baseline value resulted when they had been immobilized with etorphine / xylazine.

Respiratory minute volume

There were no significant differences between the three treatments, except at 35 minutes PDA (Fig. 4.4). At this time the respiratory minute volume was lower in the goats immobilized with etorphine as compared to immobilization with etorphine / xylazine. The administration of diprenorphine in all animals, resulted in a return of the respiratory minute volume to baseline values

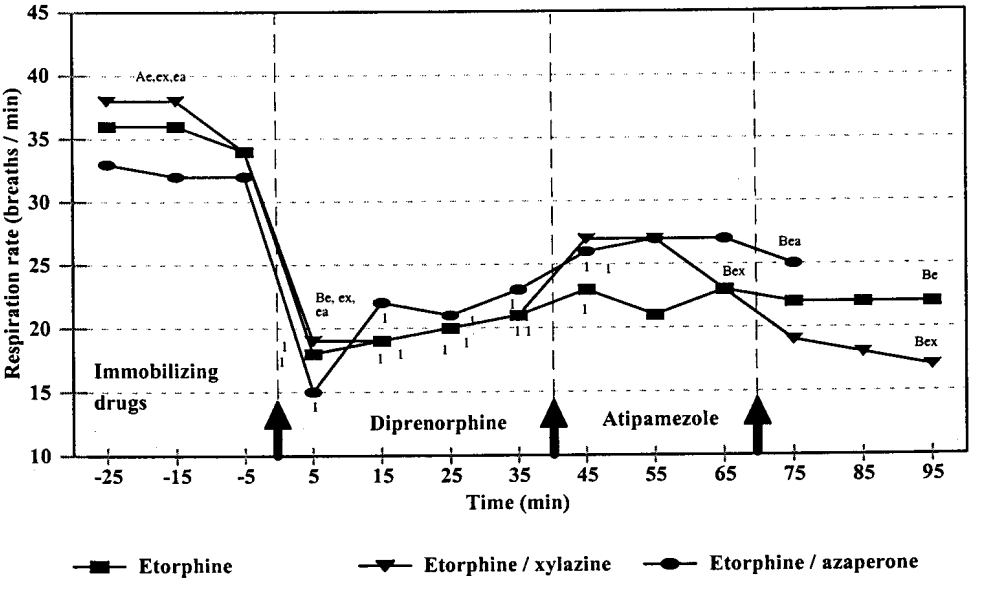

Fig. 4.5 Mean respiratory rate in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

There were no significant differences between the three treatments (Fig 4.5).

Tidal volume

The administration of etorphine resulted in no significant changes to tidal volume. The decrease in tidal volume after etorphine / xylazine became significant at 35 minutes PDA and the decrease due to etorphine / azaperone at 15 minutes (Fig. 4.6).

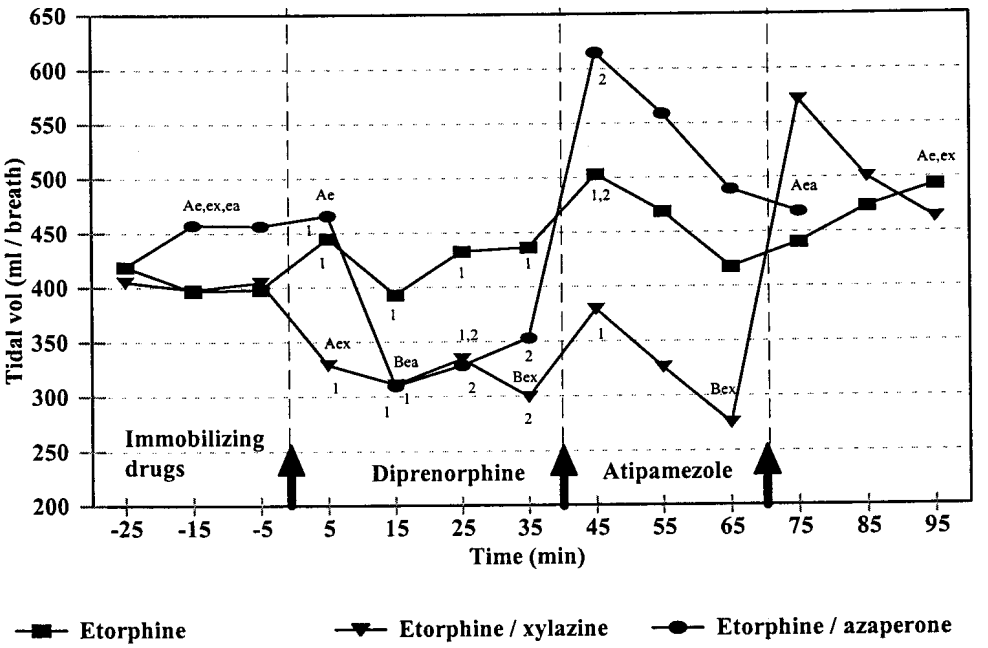

Fig. 4.6 Mean tidal volume in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Alveolar ventilation

All three treatments caused significant decreases in alveolar minute ventilation (Fig. 4.7). The alveolar minute ventilation was significantly lower in animals given etorphine / xylazine when compared to those injected with etorphine. The alveolar minute ventilation volume after etorphine / azaperone was found to be between those resulting from etorphine or etorphine / xylazine and were not significantly different from either.

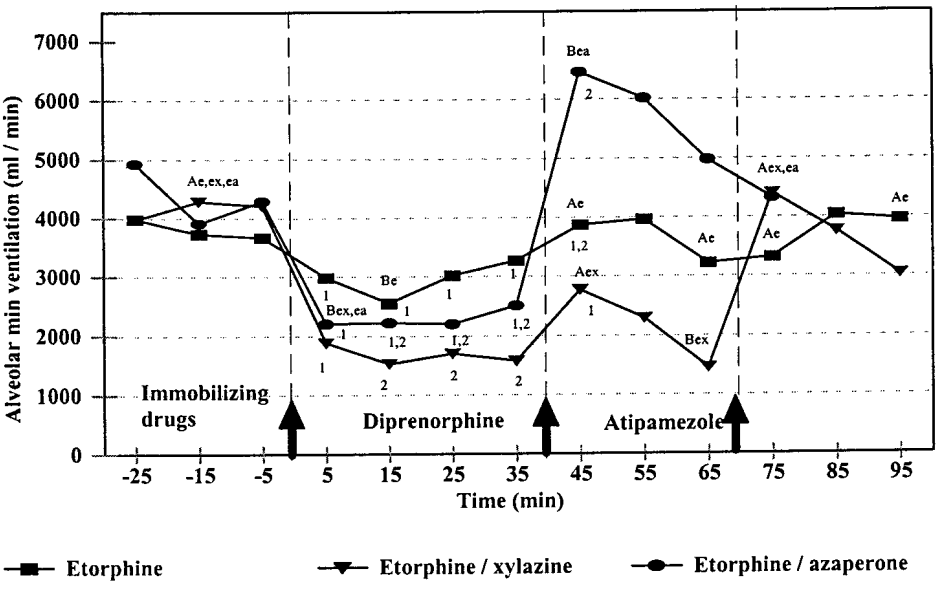

Fig. 4.7 Mean alveolar minute ventilation in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing dugs, diprenorphine and atipamezole were injected, respectively.

The administration of diprenorphine caused a return of alveolar minute ventilation to baseline values when the goats had been immobilized with etorphine or etorphine / xylazine. When they had received etorphine / azaperone, the alveolar minute ventilation became markedly elevated after the antidote.

Physiological shunt fraction

The increase in percentage physiologic shunt after etorphine was not significant (Fig. 4.8), whereas the increases due to etorphine / xylazine and etorphine / etorphine were significant. The increase after etorphine / xylazine was significantly greater than the increases after either etorphine or etorphine / azaperone. There were no significant differences between the changes induced by etorphine and etorphine / azaperone.

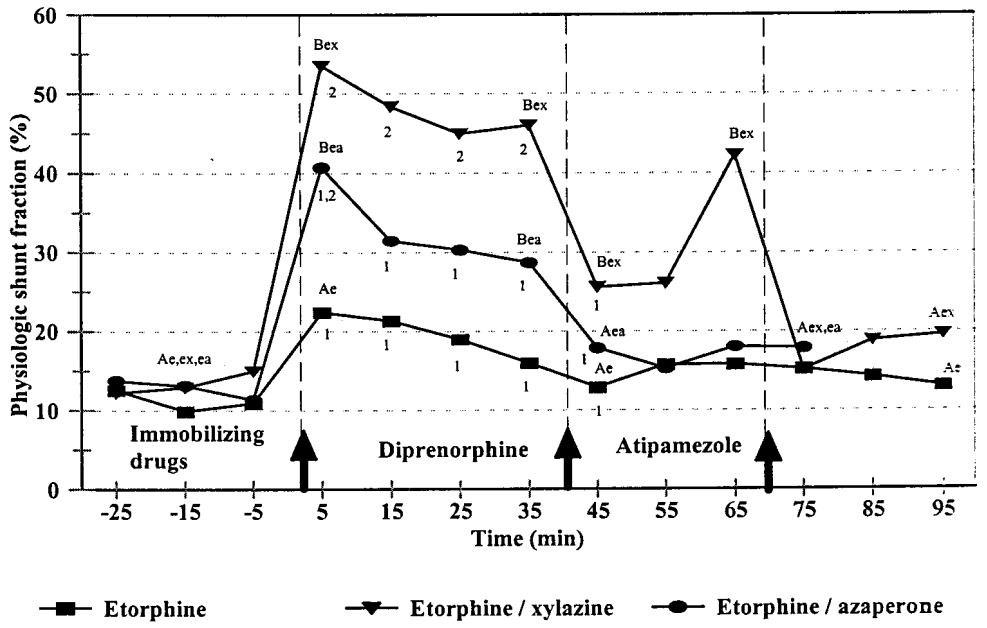

Fig. 4.8 Mean physiologic shunt fraction in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

When the goats were immobilized with etorphine or etorphine / azaperone, the administration of diprenorphine resulted in the physiological shunt fraction returning to baseline values within

five minutes. When animals had been given etorphine / xylazine, the percentage shunt fraction decreased but was still significantly elevated five minutes after administration of diprenorphine.

Physiologic dead space ventilation fraction

A significant decrease in the physiologic dead space ventilation was measured after etorphine and etorphine / azaperone. Etorphine / xylazine had an opposite effect; the physiological dead space ventilation increased significantly and was significantly greater than after etorphine but not after etorphine / azaperone. The changes due to etorphine or etorphine / azaperone were not significantly different (Fig. 4.9).

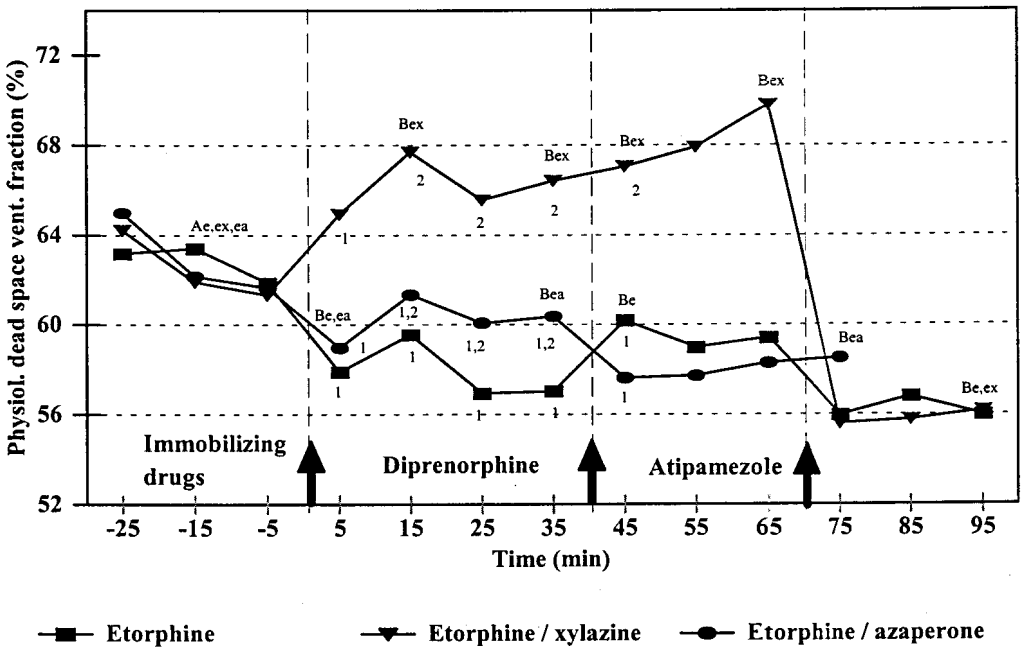

Fig. 4.9 Mean physiologic dead space ventilation fraction in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

The injection of diprenorphine did not result in significant changes to the percentage physiologic dead space ventilation in the goats when immobilized with any of the three treatments.

4.2 DISCUSSION

4.2.1 Introduction

The PaO_2 values recorded for the goats at rest were, not unexpectedly, lower than reported values as the trial was conducted in Pretoria where the mean barometric pressure is 660 mm Hg[76] (Table 4.1). The slightly elevated $PaCO_2$ values compared to the range (35.3 to 41.1 mm Hg) reported for standing unsedated goats, may have been due to rebreathing of expired air within the face mask or to a reduction of the alveolar ventilation as a result of increased dead space (Table 4.1).

The mean respiratory minute volumes at rest recorded in this trial were similar to reported values (10 540 and 11 900 ml / min)[76] (Table 4.2) but the respiratory rates were higher than those reported for goats (13.6 to 26 breaths / min.) by others[76]. The large standard deviation suggests that there was a marked variation between individuals and possibly differences within the same individual at different sample collection times (Table 4.2). The elevated mean $PaCO_2$ values, suggests that although the goats were panting, the breaths were shallow and gaseous exchange was not affected. The mean tidal volume was slightly lower than reported values of 470 to 602 ml / breath[76](Table 4.2).

Table 4.1 **The mean $PaCO_2$, PaO_2 and arterial pH of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation)**

Time	PaO_2	$PaCO_2$	Arterial pH
(min.)	(mm Hg)	(mm Hg)	
-25	80.51 (± 4.21)	41.91 (± 1.92)	7.397 (7.374 - 7.422)
-15	78.99 (± 4.81)	41.32 (± 2.15)	7.399 (7.374 - 7.426)
-5	82.2 (± 5.83)	41.03 (± 2.42)	7.400 (7.374 - 7.427)

The alveolar minute volume at rest expressed as a percentage of respiratory minute volume was lower than expected; 35.87 ± 7.58 % at -25 minutes, 37.5 ± 7.26 % at -15 minutes and 37.55 ± 6.51 % at -5 minutes (Table 4.3). It is reported that about 66 percent of the volume of humid inspired air is generally involved in alveolar ventilation[93]. This reduced alveolar ventilation was possibly the result of the increase in dead space caused by the face mask; or the fact that the animals were panting. It did not however affect the resting $PaCO_2$ or PaO_2 which are within the range of partial pressures expected.

Table 4.2 **The mean minute respiratory volume, respiration rate and tidal volume of the goats standing at rest, before the administration of the immobilizing drug combinations (± = Standard deviation)**

Time	Respiration Rate	Tidal Volume	Respiratory Minute Volume
min.	breaths / min.	ml / breath	ml / min.
- 25	35.56 (± 25.03)	414.19 (± 172.27)	12778.98 (± 6378.11)
-15	35.72 (± 28.40)	417.06 (± 137.65)	12604.08 (± 6607.11)
-5	33.28 (± 19.94)	419.51 (± 130.74)	12414.10 (± 4580.14)

The physiologic shunt fraction was estimated in this study using an algorithm and constants that apply in cattle. In dogs and humans the physiologic dead space ventilation fraction is reported to be approximately 35% of tidal volume but may be approximately 50% in larger species such as the horse and the cow[76]. In the experimental goats, the baseline percentage physiologic dead space ventilation values were higher than this, once again probably as a result of the artificial increase in anatomical dead space by the mask (Table 4.3).

Table 4.3 The mean alveolar minute ventilation, physiologic shunt fraction and physiologic dead space ventilation fraction of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation)

Time	Alveolar minute ventilation	Physiologic shunt fraction	Physiologic dead space ventilation fraction
(min.)	(ml / min.)	(%)	(%)
-25	4793.88 (± 2688.34)	12.84 (± 4.8)	64.13 (± 7.58)
-15	4414.99 (± 1459.41)	11.97 (± 5.57)	62.5 (± 7.26)
-5	4498.6 (± 1222.09)	12.4 (± 6.71)	61.61 (± 6)

4.2.2 Etorphine

Etorphine resulted in a significant decrease in the PaO_2 and a significant increase in the $PaCO_2$ within five minutes of administration (Fig. 4.1 & 4.2). The PaO_2 remained significantly depressed for the duration of the immobilization, whereas the $PaCO_2$ gradually returned to the baseline value. Similar results are reported when goats were administered 0.04 mg/kg of etorphine intramuscularly[50]. A decrease in PaO_2 and an increase in $PaCO_2$ resulted, and was followed by a progressive return of both partial pressures to their respective baseline values. The changes in

arterial pH closely followed those in the $PaCO_2$. The immobilized goats developed a respiratory acidosis (Fig. 4.3).

The results indicate that the decrease in PaO_2 and the increase in $PaCO_2$ were due to significant decreases in respiratory minute volume and alveolar minute ventilation (Fig. 4.4 & 4.7). These decreases occurred as a result of a fall in the respiratory rate, rather than a change to tidal volume (Fig. 4.5 & 4.6). The percentage physiologic shunt did not change significantly and therefore did not contribute to the changes observed in the blood gases (Fig. 4.8). During the same time period, the percentage physiologic dead space ventilation decreased but is unlikely to have contributed to the changes recorded in the PaO_2 and $PaCO_2$ (Fig. 4.9). An increase in PaO_2 and a decrease in $PaCO_2$ is expected with a decrease in dead space ventilation.

Respiratory depression is reported as the principle side effect of the opioids in a wide variety of immobilized animals[43,104]. Etorphine has an inhibitory effect on the brain stem respiratory centres, reducing their sensitivity to carbon dioxide and results in a decreased respiratory drive[59,91]. Although opioids are reported to depress all phases of respiration, their primary effect is a reduction of the rate of breathing[59], as was recorded in this investigation (Fig. 4.5). In goats, Heard *et al*[59] report that 0.02 mg/kg of etorphine administered intravenously resulted in a significant bradypnoea within 2.5 minutes. Etorphine administered to goats premedicated with either triflupromazine or triflupromazine and atropine, resulted in a decrease in respiratory rate[106]. Similar results are reported in Saanen goats given etorphine plus acepromazine[77]. These reports do not indicate the changes to tidal volume, respiratory minute volume or alveolar minute ventilation.

Respiratory volumes in the immobilized 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; an obstruction of the upper airway resulting in an increased resistance to airflow[76,118]; or the development of ruminal bloat[76].

There is a reported rise in intraruminal and intraperitoneal pressure in cattle that assume sternal recumbency, this forces the diaphragm into the chest cavity resulting in an increase in respiratory resistance[102]. A reported increase in measured airway resistance took place when goats assumed sternal recumbency after immobilization with etorphine and acepromazine[77].

The effects the change in body position had on respiratory function in this investigation, were not determined. The goats went down into sternal recumbency after the administration of each of the three immobilizing drug treatments and this position was maintained in all the immobilized animals. There were no differences in the postural changes that occurred and thus the effects on respiratory function were similar in all cases.

The head of each goat was 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 occurred[70]. Maintaining the head and neck position also allowed the unobstructed passage of gas produced in the rumen and prevented the development of ruminal bloat.

The initial etorphine induced depression of respiratory function in the immobilized goats was followed by a gradual recovery. Respiratory minute volume and alveolar minute ventilation improved significantly, due to increases in respiratory rate and tidal volume, between 15 and 35 minutes PDA (Fig. 4.4, 4.7, 4.5 & 4.6). This improvement in respiratory function may have resulted from the hypoxic stimulation of the chemoreceptors which are reported to be still effective once opioids have decreased their responsiveness to carbon dioxide[90]. Although the stimulation of respiration by the peripheral chemoreceptors is reported to become marked only at a PaO_2 of between 20 to 40 mmHg in man[39] and below 60 mmHg in horses[76], 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 hypercapnoea[76]. In addition to these changes it is likely that the reduction in the pharmacodynamic effects of etorphine as a result of its metabolism, also resulted in the improvement in respiratory function over time. The onset of action of etorphine in wildlife is reported to take place 2 to 8 minutes after intramuscular administration. The peak effects, depending on the rate of absorption, follow in 15 to 30 minutes. The duration of effect is approximately one hour[104]. In goats, Heard *et al*[49] 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 administration of diprenorphine to the immobilized goats resulted in a rapid return of the PaO_2 and the $PaCO_2$ to their respective baseline values (Fig. 4.1 & 4.2). Due to the changes in the $PaCO_2$, the arterial pH also returned to a level recorded prior to immobilization (Fig. 4.7). The normalization of the PaO_2 and $PaCO_2$ was due to an increase in the alveolar minute ventilation (Fig. 4.7). The PaO_2 and $PaCO_2$, and the arterial pH, were subsequently maintained at baseline

values as the alveolar minute ventilation did not undergo further significant changes for the remainder of the trial period. The results indicate that the decrease in percentage physiologic dead space ventilation, between 65 and 95 minutes PDA, assisted in maintaining the alveolar minute ventilation as the respiratory minute volume was significantly depressed during this period (Fig. 4.9 & 4.4).

The results show that diprenorphine was effective in reversing the etorphine induced respiratory depression in goats. The mechanism of action of the diprenorphine probably antagonised the action of etorphine at those receptors that result in a decreased sensitivity of the central chemoreceptors to carbon dioxide. In mice and rats, decreases in respiratory function are reported to be due to the actions of opioid agonists at mu_2-receptors[90]. The continued depression of the respiratory rate following the administration of the diprenorphine was possibly due to the fact that diprenorphine is a mixed opioid antagonist, retaining some agonist activity[104]. It is also possible that the low respiratory rate may also have been caused by residual etorphine activity.

4.2.3 Etorphine / xylazine

The administration of etorphine / xylazine resulted in highly significant and rapid changes to both PaO_2 and $PaCO_2$ (Fig. 4.1 & 4.2). Within five minutes of injecting this drug combination, the PaO_2 had decreased to a minimum value and the $PaCO_2$ had increased. For the remainder of the immobilization period, neither the PaO_2 nor the $PaCO_2$ varied significantly. The changes to both these blood gases, where significantly greater than those resulting from the administration of etorphine on its own.

The arterial pH varied together with the changes in the $PaCO_2$ and was significantly lower during the period of immobilization in those animals given etorphine / xylazine when compared to those that were given etorphine (Fig. 4.3 & 4.2).

The results indicate a number of reasons for the more extensive changes in the PaO_2 and the $PaCO_2$ in those animals immobilized with etorphine / xylazine when compared to those that were given etorphine. These include: a greater decrease in tidal volume and alveolar minute volume and significant elevations in both the physiologic shunt fraction and percentage dead space ventilation (Fig. 4.6, 4.7, 4.8 & 4.9). The differences in respiratory minute volume and respiratory rate between the two treatments were not statistically significant (Fig. 4.4 & 4.5). The results indicate that the addition of xylazine had a significant effect in compounding the etorphine induced depression of gaseous exchange within the respiratory system. It both increased the degree to which respiratory function was compromised and also appeared to prevent the spontaneous improvement that gradually occurred when etorphine was administered on its own.

An increased airway pressure has been suggested as a possible cause of the respiratory changes that occur with the administration of xylazine in ruminants. The increase in airway pressure could be attributed to either a decreased dynamic lung compliance or an increased airway resistance[55,81]. This would explain the decrease in respiratory tidal volume and the significant amount by which alveolar ventilation was further decreased[112](Fig. 4.6 & 4.7).

A decrease in lung compliance could be attributed to the development of a pulmonary oedema which results in a decrease in the inflation of alveoli[115]. Tachypnoea with open-mouth breathing or cyanosis, indicating the development of pulmonary oedema has been reported in sheep given

xylazine[65]. Celly *et al*[20] have shown that in sheep, sedative doses of xylazine result in pulmonary oedema and haemorrhage of a magnitude which would result in a considerable decrease in the PaO_2 and an increase in ventilation-perfusion mismatching within 10 minutes of intravenous administration.

Xylazine has been shown to produce a significant increase in airway pressure in sheep[81]. This increase can be prevented by the prior administration of either of the alpha$_2$-adrenoceptor antagonists idazoxan or atipamezole, suggesting that the increase is mediated via alpha$_2$-adrenoceptor activity[81,112]. The administration of prazosin, an alpha$_1$-adrenoceptor antagonist, does not prevent it from occurring[21]. There is some debate as to whether these xylazine effects are mediated by central or peripheral alpha$_2$-adrenoceptors. The injection of xylazine into the cerebrospinal fluid in the cisterna magna did not increase airway pressure[80] and ST-91, an alpha$_2$-agonist that does not cross the blood brain barrier, administered intravenously induced hypoxaemia in conscious sheep[21]. This suggests that these effects are mediated by the peripheral alpha$_2$-receptors. Xylazine has been reported to cause a direct alpha$_2$-adrenoceptor mediated effect on bronchial or bronchiolar smooth muscle[112]. Papazoglou *et al*[82], concluded from clinical trials on isolated sheep trachea that alpha$_2$-adrenoceptors exist in this tissue, and that the stimulation of these receptors by xylazine can cause tracheal contractions. It has been suggested that xylazine, rather than having a direct effect on alpha$_2$-adrenoceptors, activates pulmonary intravascular macrophages. Celly *et al*[20], have shown this to occur with sedative doses of xylazine administered to sheep. They therefore suggest, that mediators, e.g. leukotrienes, released from activated pulmonary intravascular macrophages could bring about an intense bronchoconstriction[20]. It is interesting to note that pulmonary intravascular macrophages tend to

be unique to those animals, e.g. ruminants, that manifest a hypoxaemic response to alpha$_2$-agonists[20].

It is reported that increased airway pressure and hypoxaemia in sheep resulting from the administration of xylazine, can be attenuated but not fully prevented by the administration of atropine[81,112]. Papazoglou *et al*[82], conclude from clinical trials on isolated sheep trachea that alpha$_2$-adrenoceptor agonists may act on airways in sheep directly through stimulation of peripheral alpha$_2$-receptors located in the trachea and indirectly via the central alpha$_2$-adrenergic receptor activation of parasympathetic tone.

Compared to those animals receiving etorphine, the results indicate that the inclusion of xylazine in the immobilizing drug treatment not only resulted in a greater decrease in tidal volume and alveolar minute volume but also caused significant increases in both the percentage physiologic shunt and physiologic dead space ventilation (Fig. 4.8 & 4.9). This increase in ventilation-perfusion mismatching due to alpha$_2$-agonists is reported by a number of authors[22,55,65].

Apart from the decrease in alveolar ventilation, changes in blood flow to the alveoli would contribute to the increase in ventilation-perfusion mismatching. Waterman *et al*[112], suggest that the ventilation-perfusion mismatch may be due to the presence of postsynaptic alpha$_2$-adrenoceptors in the pulmonary vasculature. Xylazine induced contraction of the vascular smooth muscles would create a redistribution of blood flow to vessels of least resistance thereby creating a mismatch of ventilation and perfusion. A fall in cardiac output due to the addition of xylazine is also thought to increase the degree of mismatching[65,112]. This is due to the fact that, the perfusion of alveoli in the various areas of the lungs is determined by the relationship between

alveolar, pulmonary arterial and venous, and interstitial pressure. Alveolar perfusion is most effective when pulmonary arterial pressure is greater than the alveolar, venous and interstitial pressures. Any drop in cardiac output may result in a fall in pulmonary artery pressure and a decrease in the perfusion of alveoli[76]. The results of this trial indicate that cardiac output was significantly reduced by the inclusion of xylazine into the immobilizing drug treatment (Fig. 5.3).

Celly *et al*[21], suggest that muscle relaxation and sedation may contribute to alpha$_2$-agonist induced hypoxaemia by altering the shape and/or function of the chest wall and diaphragm. This could cause a change in the distribution of inspired gas and matching of ventilation to perfusion throughout the lungs and the generation of an increased alveolar-to-arterial oxygen tension gradient. The increased shunt fraction could theoretically occur because of the development of segmental airway obstruction, pulmonary oedema or atelectasis, or opening up of the previously closed vasculature connections between the right and left sides of the pulmonary circulation[22].

The initial increase in the PaO_2 and decrease in the $PaCO_2$ following the administration of diprenorphine, indicates that there was an improvement in gas exchange between the alveolar air and the pulmonary blood (Fig. 4.1 & 4.2). This appears to have been due primarily to a significant decrease in the physiologic shunt fraction (Fig. 4.8). The improvements in both respiratory minute volume and alveolar minute ventilation measured at the same time were not statistically significant (Fig. 4.4 & 4.7).

The initial improvements following the administration of diprenorphine, in the partial pressures of oxygen and carbon dioxide, respiratory minute volume, alveolar minute ventilation, and percentage physiologic shunt fraction were reversed over the next the 30 minutes (Fig. 4.1, 4.2,

4.4, 4.7 & 4.8). It is possible that some of this reduction in respiratory function was due to the diprenorphine which is recognised as a mixed antagonist[104] or residual effects of the etorphine. It is more probable that the effects of the xylazine, which had not yet been antagonised, were responsible for returning the respiratory function to a depressed state similar to that prior to the administration of the diprenorphine. Numerous reports indicate that xylazine can cause a mild to severe decrease in PaO_2 with increases in $PaCO_2$ in sheep[19,81,91] and other ruminants including cattle, calves[13,24,33,66] and goats[69]. As has been discussed, it is proposed that in sheep these changes are due to an increase in airway pressure[55,81] and ventilation-perfusion mismatching[22,55,65].

The administration of atipamezole resulted in a return of the PaO_2 to its baseline value and a significant improvement in the $PaCO_2$ (Fig.4.1 & 4.2). Both the respiratory minute volume , due to a large increase in tidal volume, and the alveolar minute volume initially returned to their respective baseline values (Fig. 4.4, 4.6 & 4.7). There were also significant improvements in the physiologic shunt and dead space ventilation fractions (Fig. 4.8 & 4.9). These changes support the suggestion that the continued respiratory depression following the administration of the diprenorphine was due to the xylazine.

The decreases in both respiratory minute volume and alveolar minute ventilation towards the end of the trial (75 to 95 min PDA) are probably best explained by the "sleep-like" state that the goats adopted during this period (Fig. 4.4 & 4.7). Due to their decreased activity, oxygen consumption and carbon dioxide production would have been reduced compared to the period prior to immobilization. The percentage physiologic dead space ventilation was significantly lower during this period compared to prior to the administration of the etorphine / xylazine (Fig.4.9).

Therefore, some of the effects due to a decrease in alveolar minute ventilation would have been offset by a decrease in the fraction of the tidal volume ventilating physiologic dead space.

It is difficult to explain the fluctuations in the PaO_2 and $PaCO_2$ seen towards the end of the trial period (Fig. 4.1 & 4.2). It is possible they are as a result of the different body mechanisms that control these two blood gas values, re-establishing a steady state[116]. This may be particularly pertinent considering the duration of the immobilization and the number of drugs administered to the goats during this period. In humans it is reported that, postoperative hypoxaemia induced in part by gas exchange abnormalities during anaesthesia may persist for hours or days[63].

4.2.4 Etorphine / azaperone

The immobilization of the goats with etorphine / azaperone caused a significant decrease in the PaO_2 and increase in the $PaCO_2$, as in the case of the other two drug treatments used (Fig. 4.1 & 4.2). These changes were not significantly different from those resulting from the administration of etorphine, but were significantly less than those that followed the injection of etorphine / xylazine. These results indicate that the utilization of azaperone with etorphine did not affect the efficiency of respiration more severely than when etorphine on its own was administered.

It has been suggested that azaperone may antagonise respiratory depression caused by opioids[64,86]. Azaperone administered on its own is reported to improve respiration in dogs and pigs[14,87]. However, the combination of droperidol and fentanyl when administered to dogs resulted in a

decreased minute respiratory volume and respiratory acidosis[32]. In these clinical trials, azaperone was shown to have no effect in antagonising the respiratory depression due to etorphine in goats.

The changes in respiratory minute volume, alveolar minute ventilation and percentage physiologic dead space ventilation during the period of immobilization that resulted from the administration of etorphine / azaperone were not significantly different from those caused by either etorphine or etorphine / xylazine (Fig. 4.4, 4.7 & 4.9). The changes to these measures due to etorphine / azaperone were of a greater magnitude than those caused by etorphine but less that those resulting from etorphine / xylazine. Therefore, it was expected that the changes in PaO_2 and $PaCO_2$ resulting from etorphine / azaperone would similarly lie between those resulting from etorphine and etorphine / xylazine. This was not found to be the case. The PaO_2 and $PaCO_2$ measured after etorphine / azaperone were not significantly different from the respective values resulting from the administration of etorphine, but were significantly different from those values caused by etorphine / xylazine (Fig. 4.1 & 4.2). This appears to be the result of different effects the immobilizing drug treatments had on the physiologic shunt fraction (Fig. 4.8). The use of xylazine in combination with etorphine caused a significant increase in physiologic shunting in the immobilized animals, whereas the use of azaperone did not. This difference is possibly due to a difference in effect these two drugs have on pulmonary vasculature and / or cardiac output. Xylazine, an $alpha_2$-agonist, potentially causes vascular smooth muscle contractions and it is also reported to reduce cardiac output[65,112]. Azaperone, may block the activity of dopamine at dopamine receptors in certain vascular beds as is reported to occur following the administration of haloperidol[1]. Azaperone is also an antagonist of peripheral $alpha_1$-adrenoceptors[91].

The immediate improvement in respiratory function and the return of the PaO_2 and the $PaCO_2$ to their respective baseline values following the administration of the diprenorphine, further supports the proposal that azaperone had little or no effect in compounding the respiratory depression due to etorphine (Fig. 4.1 & 4.2). As an opioid antagonist, diprenorphine is expected to antagonise respiratory depression due to etorphine. The respiratory centre responds to an elevated $PaCO_2$, returning it and the depressed PaO_2 to their respective pre-immobilization values. There was also no residual respiratory depression following the administration of the diprenorphine, as occurred with the etorphine plus xylazine immobilizing combination.

Despite the $PaCO_2$ returning to baseline values, the goats were still acidotic by the end of the trial period (Fig. 4.2 & 4.3). A decrease in the standard arterial bicarbonate concentration after the administration of the diprenorphine suggests that this was due to the development of a mild metabolic acidosis.

CHAPTER 5

CARDIOVASCULAR FUNCTION

5.1 RESULTS

Refer to Appendix B for a summary of statistical analyses

5.1.1 Etorphine

5.1.1.1 Immobilization (0 to 40 min)

The administration of etorphine resulted in significant increases in both systemic mean arterial blood pressure and total peripheral resistance (Fig. 5.1 & 5.2). They reached maximum values at 5 and 15 minutes PDA, respectively. Both, did not undergo further significant changes during the remaining period of the immobilization.

The cardiac output declined significantly within five minutes of injecting the etorphine and remained depressed for the duration of the immobilization (Fig. 5.3). This decrease in cardiac output was due to a significant reduction in heart rate, rather than a change to stroke volume (Fig. 5.4 & 5.5).

5.1.1.2 Recovery (40 to 95 min)

Following the administration of diprenorphine, the mean arterial blood pressure, total peripheral resistance and cardiac output returned to their respective baseline values (Fig. 5.1, 5.2 & 5.3).

5.1.2 Etorphine / xylazine

5.1.2.1 Immobilization (0 to 40 min)

Within five minutes of the administration of etorphine / xylazine, the systemic mean arterial blood pressure had fallen significantly and although it subsequently did not change significantly, a minimum value was recorded immediately prior to the administration of the diprenorphine (Fig. 5.1). At the same time the total peripheral resistance did not change significantly in the immobilized goats (Fig. 5.2). The cardiac output declined becoming significantly lower than the baseline value at 35 minutes PDA (Fig. 5.3). This decrease was due to both a fall in stroke volume and heart rate, neither of which were statistically significant (Fig. 5.4 & 5.5).

5.1.2.2 Recovery (40 to 95 min)

The injection of diprenorphine caused a partial and temporary increase in the systemic mean arterial blood pressure which later returned to the baseline value following the injection of atipamezole (Fig. 5.1). Neither total peripheral resistance nor systemic mean arterial blood pressure showed any significant response to the diprenorphine (Fig. 5.2 & 5.3). Atipamezole

caused the peripheral resistance to increase significantly and remain persistently elevated above the baseline value. By comparison, the cardiac output increased temporarily but was nevertheless still significantly depressed by the end of the trial period. The changes in cardiac output were due to variations in both the heart rate and stoke volume (Fig. 5.4 & 5.5).

5.1.3 Etorphine / azaperone

5.1.3.1 Immobilization (0 to 40 min)

The administration of etorphine / azaperone was followed by a progressive decline in the systemic mean arterial blood pressure which became significantly depressed 15 minutes PDA and reached a minimum value measured immediately prior to the injection of the diprenorphine (Fig. 5.1). The total peripheral resistance also underwent a gradual decline over time and this became significant at 35 minutes PDA (Fig. 5.2). The cardiac output initially increased but this change was not significant (Fig. 5.3).

5.1.3.2 Recovery (40 to 75 min)

The administration of diprenorphine caused rapid and significant increases in both systemic mean arterial blood pressure and cardiac output (Fig. 5.1 & 5.3). The blood pressure returned to baseline values and the cardiac output became significantly elevated as a result of a significant increase in heart rate (Fig. 5.4). A small decrease in stoke volume took place at the same time.

The total peripheral resistance did not show any change after the diprenorphine had been given and continued to decrease (Fig. 5.2). It rose slightly during the last 20 minutes of the trial.

5.1.4 Comparisons between the three treatments

5.1.4.1 Induction, Immobilization and recovery (- 5 min to 45 min)

Systemic mean arterial blood pressure

The three immobilizing drug treatments resulted in significant changes to the systemic mean arterial blood pressure (Fig. 5.1). After the administration of etorphine the blood pressure increased significantly above the baseline values and remained so for the duration of the immobilization. The opposite occurred after either etorphine / xylazine or etorphine / azaperone, in both cases the blood pressure fell significantly. The blood pressures resulting from these latter two immobilizing drug treatments did not differ significantly between 15 and 35 minutes PDA. The administration of diprenorphine resulted in the blood pressures returning to their respective baseline values in animal immobilized with etorphine and etorphine / azaperone whereas the pressure after etorphine / xylazine, despite a moderate increase, remained significantly lower than the baseline value.

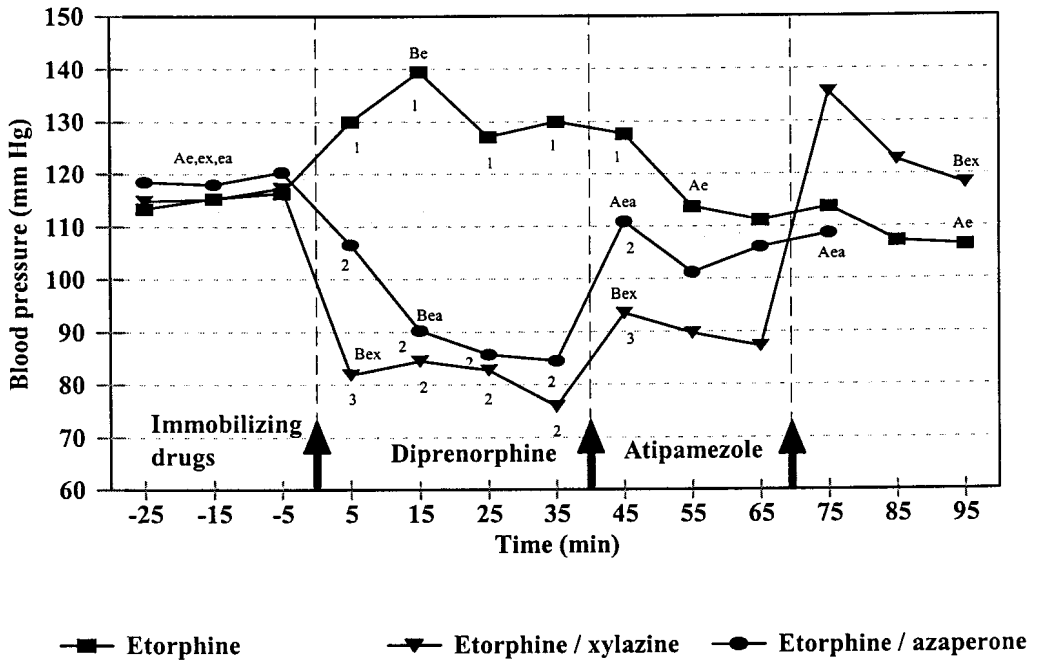

Fig. 5.1 Mean systemic mean arterial blood pressure in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Total peripheral resistance

The administration of etorphine resulted in a rapid and marked elevation in total peripheral resistance, etorphine / xylazine had no significant effect and etorphine / azaperone was followed by a gradual but significant decline in resistance over time (Fig. 5.2). The total peripheral resistance after the injection of etorphine / azaperone was significantly different from that measured after etorphine but did not differ significantly from that following etorphine / xylazine. The differences in total peripheral resistance due to etorphine and etorphine / xylazine were significant, except at 25 minutes PDA. The peripheral resistance in etorphine treated animals and those given etorphine / xylazine returned to baseline values

after diprenorphine was administered. No change occurred in those animals immobilized with etorphine / azaperone.

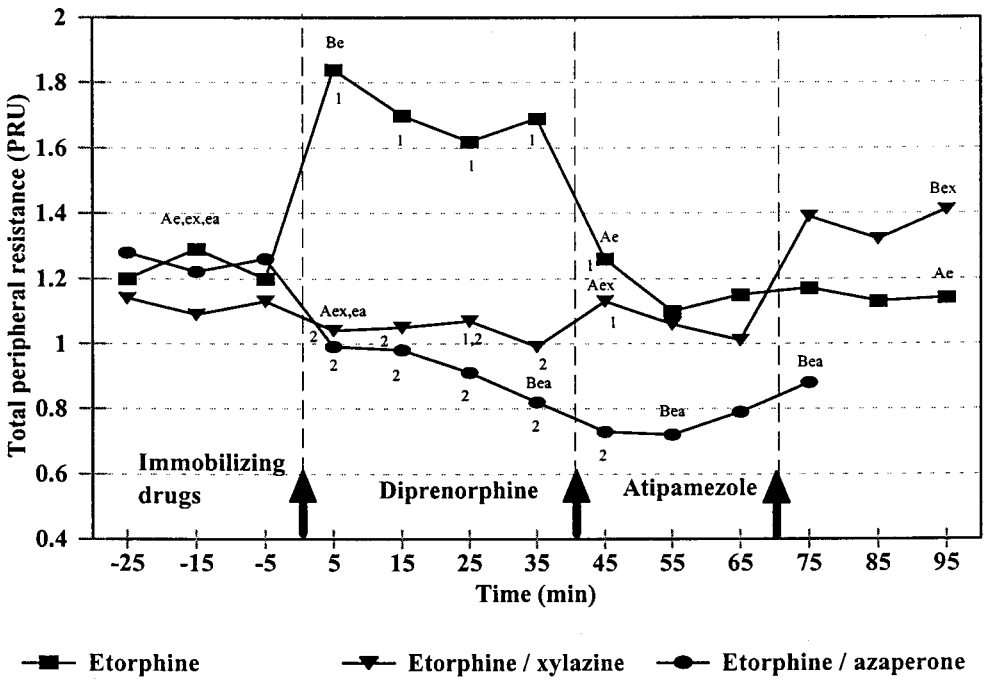

Fig. 5.2 Mean total peripheral resistance in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Cardiac output

Etorphine administered on its own or in combination with xylazine resulted in significant decreases to cardiac output. The combination of etorphine with azaperone had no significant effect (Fig. 5.3). There were significant differences between the treatments at 5 and 35 minutes PDA. At these times etorphine and etorphine / xylazine resulted in a significantly lower cardiac

outputs than etorphine / azaperone. The cardiac outputs resulting from etorphine and etorphine / xylazine were not significantly different from each other during the period of immobilization.

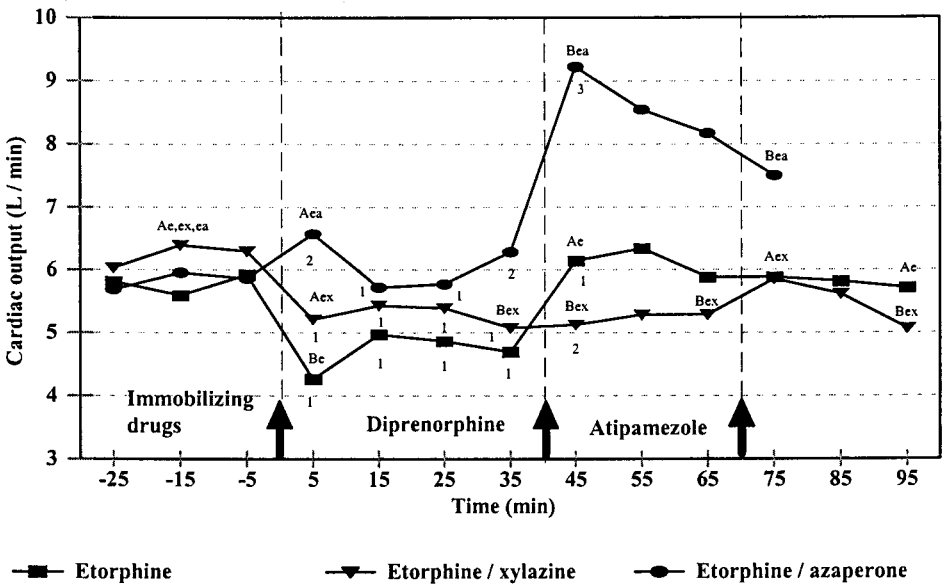

Fig. 5.3 Mean cardiac output in goats treated with different immobilizing drug combinations (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each drug combination. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which immobilizing drug combinations, diprenorphine and atipamezole were injected, respectively.

The administration of diprenorphine was followed by various results. When the goats were immobilized with etorphine the cardiac output returned to the baseline value, no change occurred in animals given etorphine / xylazine and in etorphine / azaperone treated animals the cardiac output increased to above the baseline value.

Heart rate

The administration of etorphine resulted in a significant decrease in heart rate whereas etorphine given in combination with xylazine or azaperone had no significant effects (Fig. 5.4). The administration of diprenorphine resulted in significant increases in heart rates when the goats were injected with either etorphine or etorphine / azaperone. No significant change occurred in animals immobilized with etorphine / xylazine.

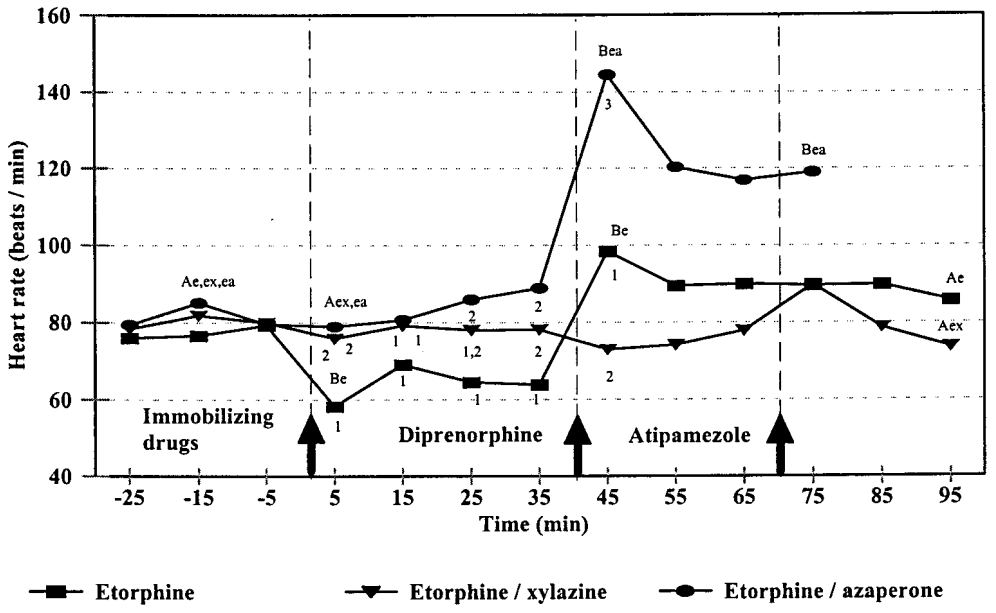

Fig. 5.4 Mean heart rate in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Stroke volume

The stroke volumes due to the three treatments were variable but seldom significantly different (Fig. 5.5).

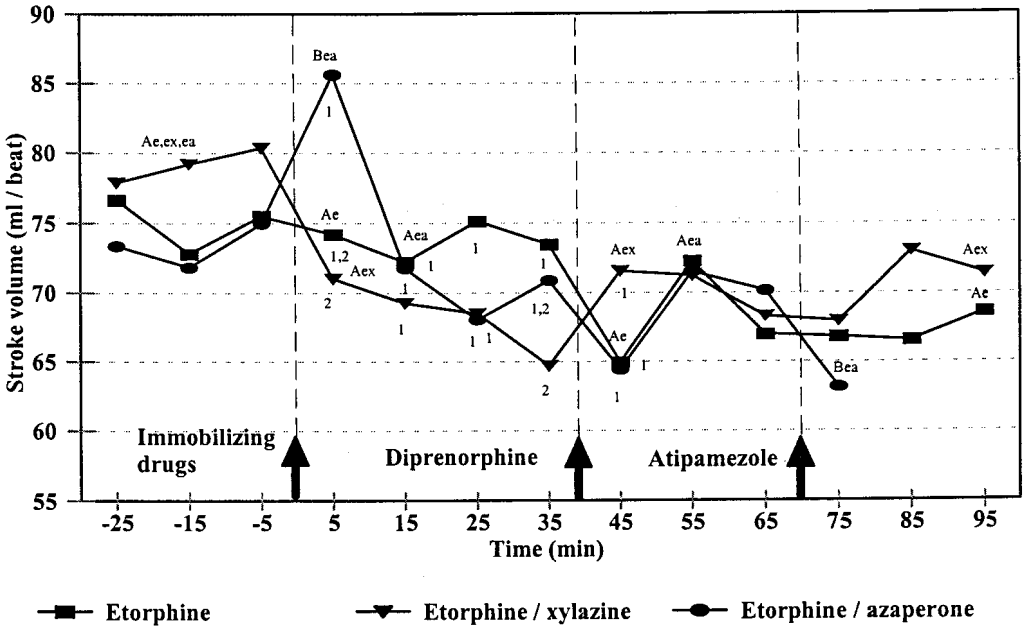

Fig. 5.5 Mean stroke volume in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

5.2 DISCUSSION

5.2.1 Introduction

The resting systemic mean arterial blood pressures measured in the goats in this trial were similar to the 102 mm Hg reported for goats by Heard *et al*[49](Table 5.1). Others report a blood pressure of 114 to 124 mm Hg [69]. Mean arterial blood pressures of 114 mm Hg in sheep and 120 mm Hg in cattle have been reported[89].

The calculated total peripheral resistance in the goats was lower than the approximate 1.4 to 1.6 peripheral resistance units (PRU) reported by Heard *et al*[50] (Table 5.1). Their goats were, however, not habituated to the experimental procedures and were restrained in slings. This suggests that the higher total peripheral resistance they measured, may have been due to an increase in sympathetic tone.

Table 5.1 The mean systemic mean arterial blood pressure and total peripheral resistance of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation)

Time (min.)	Systemic Mean Arterial Blood Pressure (mm Hg)	Total Peripheral Resistance (PRU)
-25	115.56 (± 12.1)	1.21 (± 0.18)
-15	116.17 (± 10.8)	1.2 (± 0.24)
-5	118 (± 13.27)	1.2 (± 0.2)

Although, the cardiac output varies somewhat between species it can be estimated at approximately 10% of the body mass (cardiac output = $0.1017 \times kg^{0.9988}$)[95]. The mean cardiac output measured during this study in goats standing at rest was higher than the calculated value of 5.45 ± 0.24 litres per minute (Table 5.2). Despite this, the mean cardiac output of these goats probably represented the volume expected in these animals at rest.

A heart rate of 75 beats per minute[95] and a range of 70 to 80 beats per minute[89] have been reported for goats at rest. The mean heart rates of the trial goats were similar (Table 5.2). The stroke volume was estimated from the measured cardiac output and heart rate (Table 5.2).

Table 5.2 **The mean cardiac output, heart rate and stroke volume of the goats standing at rest, before the administration of the immobilizing drugs (± = Standard deviation)**

Time (min.)	Cardiac output (Litres / min.)	Heart Rate (beats / min.)	Stroke Volume (ml / beat)
-25	5.84 (± 0.91)	77.91 (± 13.57)	75.94 (± 10.89)
-15	5.98 (± 0.95)	81.12 (± 14.19)	74.59 (± 11.28)
-5	6.02 (± 0.83)	79.54 (± 13.09)	76.93 (± 12.91)

5.2.2 Etorphine

The administration of etorphine to the goats resulted in increases in both systemic mean arterial blood pressure and total peripheral resistance, and they remained elevated for the duration of the immobilization (Fig. 5.1 & 5.2). At the same time cardiac output decreased due to a drop in heart rate rather than a lowering of stroke volume (Fig. 5.3, 5.4 & 5.5). Heard *et al*[50], report similar results in goats immobilized with comparable doses of etorphine (20 and 40 µg/kg) administered intramuscularly. A significant increase in mean systemic arterial pressure occurred within two and a half minutes in goats after 0.02 mg/kg intravenous etorphine. A decrease in the heart rate took place at the same time. This was found not to be statistically significant[49].

The results of these clinical trials and those of the above authors, suggest that etorphine results in an increase in sympathetic tone in goats, with constriction of small arteries and arterioles, and a rise in the total peripheral resistance[35]. It has been suggested that increased sympathetic nervous system activity during opioid immobilization could be attributed to restraint-induced stress,

hypoxaemia, hypercapnia, pain, specific receptor mediated effects or a combination of these[50]. The animals in this study were habituated to the procedures and not restrained. It is unlikely that the moderate decrease in PaO_2 and increase in $PaCO_2$ that occurred following the administration of etorphine caused a significant change in blood pressure, as their stimulation of the vasomotor centre and their direct peripheral effects would tend to cancel each other out[29,79]. The animals experienced no pain, except at the time of injection of the etorphine. Therefore, the results suggest that etorphine had more specific receptor mediated effects in increasing sympathetic tone. In rats centrally mediated hypertension is related to activation of sympathetic tone mediated by central opiate receptors[92]. It is also possible that the pressor response was secondary to etorphine induced release of vasoactive substances, such as histamine or catecholamines[54]. Whether the increase in sympathetic tone was mediated by central or peripheral opioid receptors, was not determined in this study.

The decrease in cardiac output due to a decrease in heart rate rather than stroke volume, suggests an increase in vagal tone. This may have been as a result of a baroreceptor reflex in response to the increased blood pressure, although it is well documented that opioids commonly blunt this reflex[54]. Stimulation of opiate receptors located in the brainstem have been proposed to lead to activation of the vagal-parasympathetic system and the negative chronotropic effects produced by opiate analgesics[54,92]. Apart from increasing vagal tone, it is possible that etorphine had a direct depressant action on the myocardium as has been reported in rats[92].

The administration of diprenorphine resulted in a rapid return of the systemic mean arterial blood pressure, the total peripheral resistance and the cardiac output to their respective baseline values

(Fig. 5.1, 5.2 & 5.3). These results, indicate that diprenorphine was highly effective in antagonising the cardiovascular effects of etorphine in the immobilized goats.

5.2.3 Etorphine / xylazine

The administration of etorphine / xylazine resulted in a rapid and significant decrease in the systemic mean arterial blood pressure, followed by a decrease in cardiac output that became significant at 35 minutes PDA (Fig. 5.1 & 5.3). The peripheral resistance remained unchanged (Fig. 5.2). Similarly, hypotension followed the administration of carfentanil / xylazine in sheep[19]. Carfentanil on its own has also been reported to cause hypertension in goats[49].

These results demonstrate that the administration of xylazine in combination with etorphine prevented the rise in total peripheral resistance associated with the administration of etorphine on its own. At the same time the systemic mean arterial blood pressure fell as a result of a lowering of cardiac output. Caulkett *et al*[19], suggest that the hypotension due to carfentanil / xylazine observed in sheep is caused by a decrease in peripheral resistance resulting from a severe hypoxaemia. The results from this present study differed from this finding. The total peripheral resistance did not change significantly. Etorphine / xylazine resulted in a significant decrease in the PaO_2 and increase in the $PaCO_2$ which may be expected to have influenced blood flow to the tissues. It is possible that a dilation of arterioles and precapillary sphincters due to tissue hypoxia and the release of vasodilator substances[35], may have prevented the increase in total peripheral resistance taking place. However, the interaction between these peripheral effects and the stimulation of the vasomotor centre as a result of the increased hypoxia and hypercapnea was not determined in this trial.

It is possible that the alpha$_2$-agonist activity of xylazine was responsible for preventing an increase in total peripheral resistance and therefore mean arterial blood pressure observed when only etorphine was administered. Numerous reports indicate that xylazine results in an initial transitory rise in blood pressure followed by a more extended period of hypotension in most species[9,13,67,107]. Hypertension was not measured when the etorphine / xylazine combination was given but may have been missed in the five minutes PDA before pressures were measured. It has been suggested that when xylazine is given intramuscularly peak blood concentrations are reached over an extended period of time and that this may dampen the hypertensive response[107]. The more prolonged hypotension commonly associated with xylazine is due to a decreased sympathetic tone resulting from xylazine's activation of central and presynaptic sympathetic neuronal alpha$_2$-adrenoceptors[107]. This decrease in sympathetic tone may have counteracted the pressor effect due to the etorphine with the net result being no significant change to the total peripheral resistance.

It appears that xylazine was responsible for the decrease in cardiac output observed in the immobilized goats. Xylazine is reported to cause a decrease in cardiac output due to decreased sympathetic and enhanced vagal tone[107], or as a result of a direct depressant effect on the contractility of the heart[13]. The results indicate that the decrease in cardiac output was due primarily to a drop in stroke volume, rather a slowing of heart rate (Fig. 5.5 & 5.4), suggesting that xylazine caused a depression of the myocardium rather than an increase in vagal activity.

The administration of diprenorphine in these animals resulted in a temporary increase in the systemic mean arterial blood pressure due to a slight, although non-significant, increase in total peripheral resistance, with no significant change to the cardiac output (Fig. 5.1, 5.2 & 5.3). By comparison, these variables all returned to their respective baseline values in the goats when

immobilized with etorphine. These results suggest that the xylazine was responsible for maintaining a depressed cardiac output and preventing a compensatory response in peripheral resistance to improve the systemic mean arterial blood pressure. Xylazine has a reported systemic half-life after intravenous administration of 23 minutes in sheep and 36 minutes in cattle[31]. A dose-dependent sleep-like state is usually maintained for 1 to 2 hours[107]. This suggests that at 45 minutes after intramuscular administration to goats, xylazine would still have significant pharmacodynamic activity. The significant increases in total peripheral resistance, cardiac output and systemic mean arterial blood pressure immediately following the administration of atipamezole, provides evidence that xylazine had maintained significant pharmacodynamic effects until this time (Fig. 5.2, 5.3 & 5.1).

Following the administration of atipamezole, the total peripheral resistance remained significantly elevated above the baseline value until the end of the trial (75 to 95 min. PDA) (Fig. 5.2). A decrease in cardiac output was followed by a gradual return of the systemic mean arterial blood pressure to the baseline value during this period (Fig. 5.3 & 5.1). It appears that the persistently elevated total peripheral resistance was due to atipamezole. It is a highly potent, selective and specific antagonist of centrally and peripherally located alpha$_2$-adrenoceptors[61,110], leading to activation of alpha$_1$-adrenoceptors[52], a constriction of arterioles and precapillary sphincters and an increase in peripheral resistance[109]. In humans, the infusion of atipamezole is reported to elevate blood pressure[109].

5.2.4 Etorphine / azaperone

The administration of etorphine / azaperone was followed by a progressive decline in the total peripheral resistance in the immobilized goats (Fig. 5.2). As the cardiac output did not change significantly, the mean arterial blood pressure fell progressively (Fig. 5.3 & 5.1).

The progressive decline in peripheral resistance was probably due to the blockade of peripheral alpha$_1$-adrenoceptors, a reported mechanism of action of azaperone[91]. This, preventing the tonic activity of the sympathetic vasoconstritor fibres, causing vasodilation and a decreased total peripheral resistance[29].

The administration of diprenorphine resulted in a rapid and significant increase in the cardiac output (Fig. 5.3). As there was no change in the activity of the azaperone following the administration of diprenorphine, as demonstrated by the persistent low total peripheral resistance, these results suggest that etorphine was responsible for preventing an increase in cardiac output in response to the low blood pressure during the period of immobilization (Fig. 5.2). The mechanism of action by which etorphine depressed cardiac function cannot be determined from these results. However, as has been discussed, possible mechanisms include a receptor mediated increase in vagal tone or a direct depressant effect of etorphine on the myocardium[54,92].

The total peripheral resistance remained unchanged after the diprenorphine was given. It continued to decrease until the last 20 minutes of the trial and increased thereafter (Fig. 5.2). This increase was probably due to metabolism and elimination of azaperone. Neither the half-life of

elimination nor the duration of the cardiovascular effects of azaperone have been reported for goats[34]. The progressive increase in total peripheral resistance towards the end of the trial with an associated increase in systemic mean arterial pressure resulted in the gradual decrease of the cardiac output towards the baseline value (Fig. 5.2, 5.1 & 5.3).

CHAPTER 6

OXYGEN CONSUMPTION

6.1 RESULTS

Refer to Appendix C for a summary of statistical analyses

6.1.1 Etorphine

6.1.1.1 Immobilization (0 to 40 min)

The oxygen consumption index declined significantly to reach a minimum value at 15 minutes PDA (Fig. 6.1). It then gradually increased, returning to the baseline value within 20 minutes. At the same time, neither the arterial nor the venous oxygen concentrations changed significantly (Fig. 6.2 & 6.3). There was an initial significant increase in the haemoglobin concentration and a non-significant drop in the percentage oxygen saturation (Fig. 6.4 & 6.5).

6.1.1.2 Recovery (40 to 95 min)

The oxygen consumption index did not change significantly (Fig. 6.1). Both arterial and venous oxygen concentrations increased significantly following the injection of diprenorphine and then

returned to their respective baseline values (Fig. 6.2 & 6.3). There was a temporary and significant increase in arterial haemoglobin concentration, and no significant change to oxygen saturation (Fig. 6.4 & 6.5).

6.1.2 Etorphine / xylazine

6.1.2.1 Immobilization (0 to 40 min)

The oxygen consumption index and both the arterial and venous oxygen concentrations declined significantly within five minutes following the injection of the etorphine / xylazine and did not undergo further change until the diprenorphine was administered (Fig. 6.1, 6.2 & 6.3). The arterial haemoglobin concentration fell progressively over time and was significantly lower than the baseline value at 15 minutes PDA (Fig. 6.4). The percentage arterial oxygen saturation declined rapidly and was significantly depressed prior to the administration of the diprenorphine (Fig. 6.5).

6.1.2.2 Recovery (40 to 95 min)

After the injection of diprenorphine, the oxygen consumption index declined further during the next 20 minutes (Fig. 6.1). The administration of atipamezole resulted in a temporary return to the baseline value before it decreased again. A moderate recovery occurred in both the arterial and venous oxygen concentrations following the injection of the diprenorphine but baseline values were only attained after the administration of the atipamezole (Fig.6.2 & 6.3). The haemoglobin

concentration and the percentage oxygen saturation, both returned to their respective baselines after the administration of atipamezole which had not been the case after diprenorphine (Fig. 6.4 & 6.5).

6.1.3 Etorphine / azaperone

6.1.3.1 Immobilization (0 to 40 min)

The oxygen consumption index decreased significantly within five minutes of administering the etorphine / azaperone and subsequently declined progressively reaching a minimum value prior to the administration of diprenorphine (Fig. 6.1). The arterial oxygen concentration decreased significantly and did not change significantly thereafter until diprenorphine was administered (Fig. 6.2). The venous oxygen and arterial haemoglobin concentrations did not change significantly (Fig. 6.3 & 6.4). The percentage oxygen saturation decreased significantly within five minutes and then progressively increased returning to the baseline value by 35 minutes PDA (Fig. 6.5).

6.1.3.2 Recovery (40 to 75 min)

Diprenorphine resulted in the oxygen consumption index, arterial and venous oxygen concentrations, and arterial haemoglobin concentration increasing to values significantly higher than their respective baseline values within five minutes (Fig. 6.1, 6.2, 6.3 & 6.4). They all, except the venous oxygen concentration, returned to their baseline values over the next 30

minutes. The venous oxygen concentration remained significantly elevated until the end of the trial period. The arterial oxygen saturation rapidly returned to the baseline value, following the injection of diprenorphine (Fig. 6.5).

6.1.4 Comparisons between the three treatments

6.1.4.1 Induction, Immobilization and recovery (- 5 min to 45 min)

Oxygen consumption index

All of the three treatments resulted in a significant decrease in the oxygen consumption index (Fig. 6.1). There were significant differences measured after the administration of etorphine and etorphine / xylazine at 5 and 35 minutes PDA, and between etorphine and etorphine / azaperone at 35 minutes PDA. Statistically, there were no differences between the changes in the oxygen consumption index resulting from etorphine / xylazine or etorphine / azaperone.

Diprenorphine resulted in the oxygen consumption index returning to the baseline value when the goats had been immobilized with etorphine. When they had been given etorphine / xylazine, there was a small and transient rise. The oxygen consumption index increased after diprenorphine was administered to animals given etorphine / azaperone to a value significantly higher than the baseline value (Fig. 6.1).

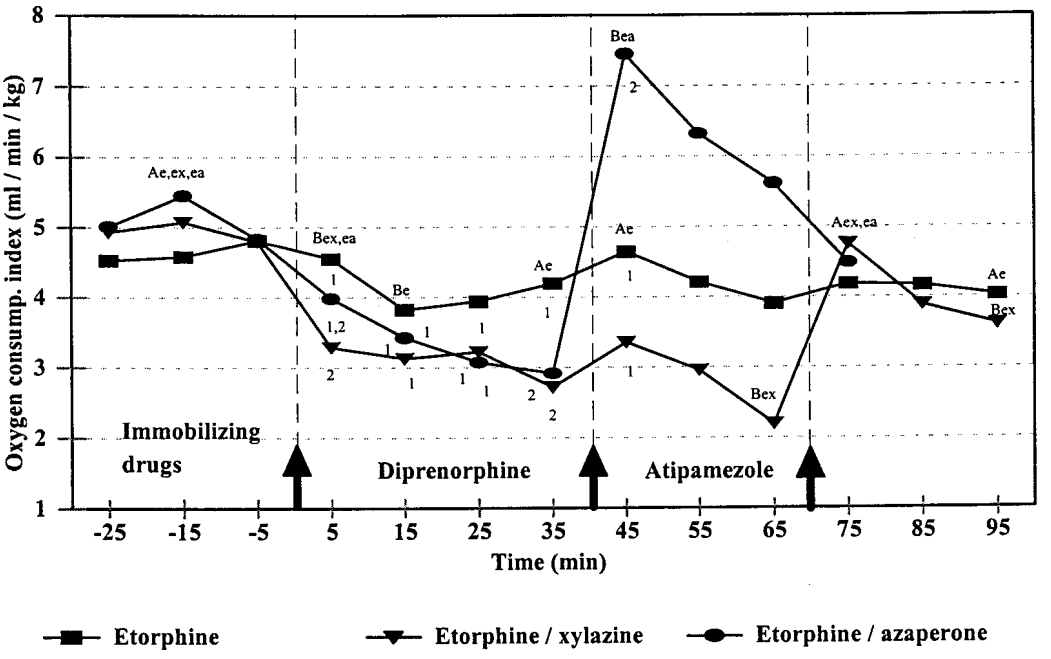

Fig. 6.1 Mean oxygen consumption index in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Arterial oxygen concentration

The arterial oxygen concentration did not change significantly following the injection of etorphine. Etorphine / xylazine and etorphine / azaperone both caused significant decreases. The drop in arterial oxygen concentration after etorphine / xylazine was significantly greater than the fall due to either etorphine or etorphine / azaperone. The changes due to etorphine or etorphine / azaperone were not statistically different, except at five minutes PDA (Fig. 6.2).

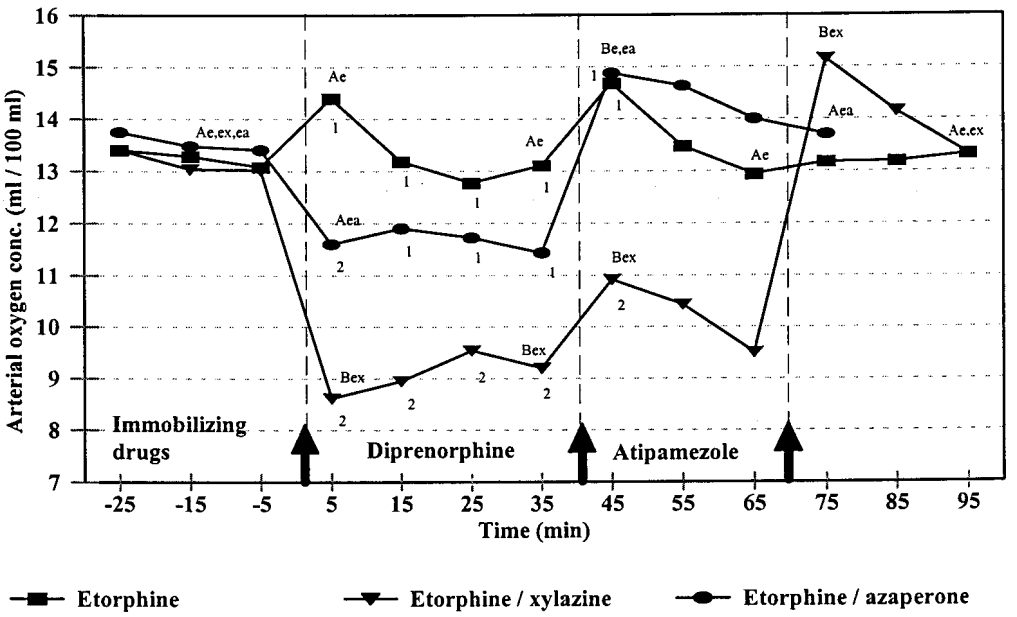

Fig. 6.2 Mean arterial oxygen concentration in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

When the goats were immobilized with either etorphine or etorphine / azaperone, the administration of diprenorphine caused the oxygen concentration to rise to above the baseline value. When they had been given etorphine / xylazine, only a partial and temporary increase occurred.

Venous oxygen concentration

The venous oxygen concentration only changed significantly in those animals that were given etorphine / xylazine (Fig. 6.3). The injection of diprenorphine caused the oxygen concentration to rise significantly above the baseline value when the goats had received either etorphine or

etorphine / azaperone. It did not result in a significant change when the goats had been immobilized with etorphine / xylazine.

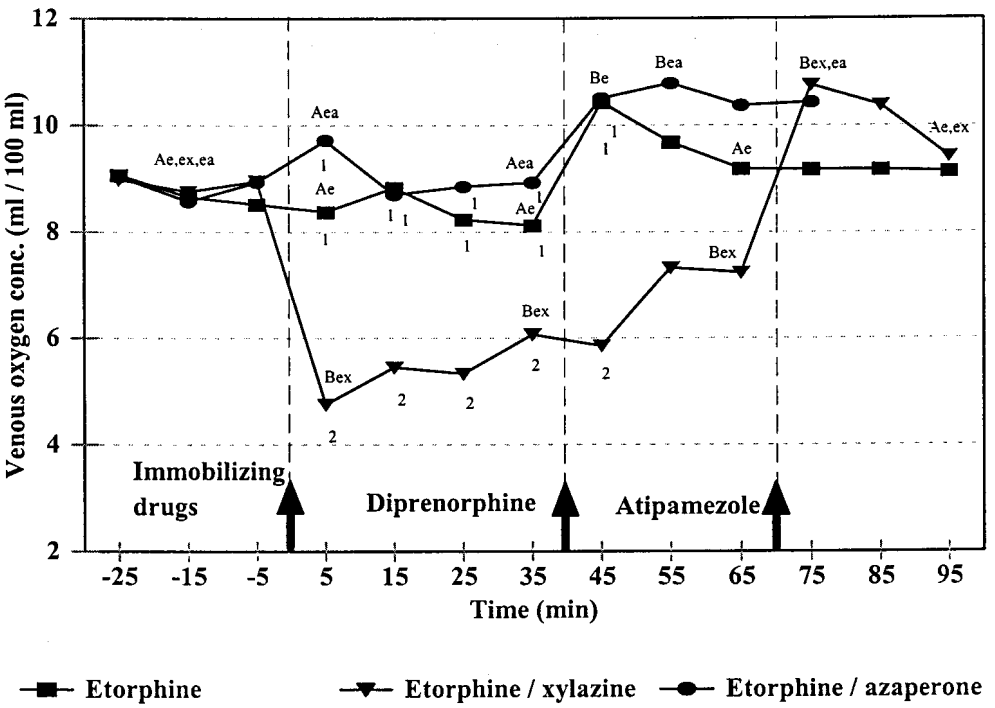

Fig. 6.3 Mean venous oxygen concentration in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Arterial haemoglobin concentration

There were no significant differences in arterial haemoglobin concentration between the three treatments, except between etorphine and etorphine / xylazine at 15 minutes PDA (Fig. 6.4). The haemoglobin concentration increased to levels significantly higher than the baseline values after the administration of diprenorphine in goats immobilized with etorphine or etorphine /

azaperone. When the animals were immobilized with etorphine / xylazine no significant change occurred.

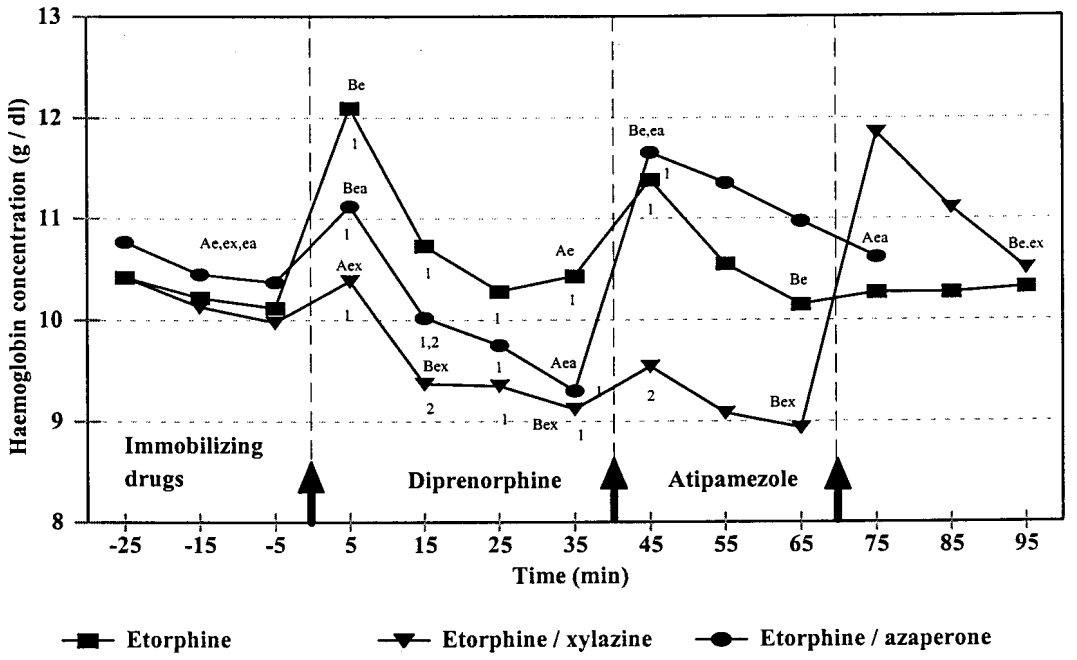

Fig. 6.4 Mean arterial haemoglobin concentration in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

Arterial oxygen saturation

The decline in oxygen saturation due to etorphine / xylazine was significantly larger than the reduction caused by either etorphine or etorphine / azaperone. The were no significant differences between the arterial oxygen saturations due to the latter two treatments (Fig. 6.5). The administration of diprenorphine resulted in the percentage oxygen saturation returning to the baseline value in goats that were immobilized with either etorphine or etorphine /azaperone. Only a partial recovery occurred in the animals that had been given etorphine / xylazine.

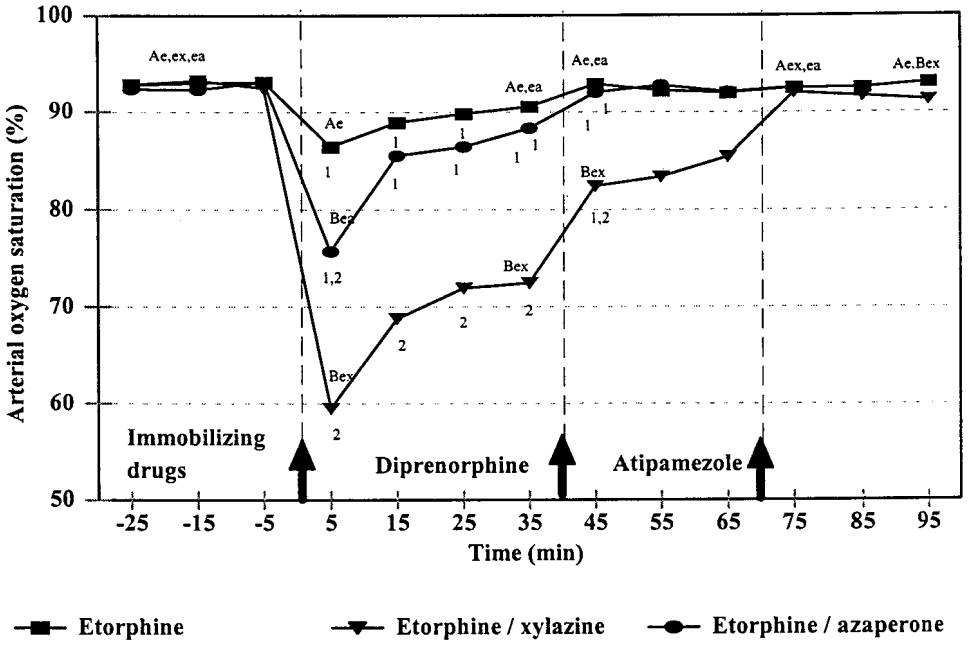

Fig. 6.5 Mean arterial oxygen saturation in goats treated with different immobilizing drugs (e - etorphine, ex - etorphine / xylazine, ea - etorphine / azaperone). Ae,ex,ea = MBVR. B, indicates a significant difference between MBVR and signalled mean values for each treatment. Statistical comparisons between the treatment groups, at the same points in time, are signalled by subscript numbers. Dissimilar numbers indicate a significant difference. Arrows, indicate times at which the immobilizing drugs, diprenorphine and atipamezole were injected, respectively.

6.2 DISCUSSION

6.2.1 Introduction

Under normal operating conditions the rate of oxygen utilization is controlled ultimately by the rate of energy expenditure within the cells[42]. A measure of oxygen consumption thus estimates the amount of energy expenditure, e.g. in humans one litre of oxygen consumed accounts for approximately 4.83 kcal of energy expended[75]. Prior to administration of the immobilizing

drugs, the energy expenditure of the goats was kept constant. As they stood quietly at rest, awake and in an environment kept at a constant temperature, it probably approached their basal metabolic requirements[75]. It can be expected that the energy requirements would decrease in the immobilized animals as a result of a decrease in physical activity[40]. The effects on the rate of metabolism of the drugs used to immobilize the goats have not been reported and were not quantified. It is likely that the changes in the oxygen consumption index measured after the administration of the immobilizing drugs and their antagonists primarily reflected the changes in the various factors that influenced the supply of the required oxygen to the tissues and not changes in the cellular energy expenditure of the goats.

The amount of oxygen that is supplied to tissues is determined by a number of interrelated factors:

a) The concentration of oxygen in the arterial blood, which depends primarily on the haemoglobin concentration and the percentage of oxygen saturation. The PaO_2 determines the level of oxygen saturation of the haemoglobin and the amount of oxygen dissolved in the blood[42,116]. The oxygen saturation is further influenced by the pH, carbon dioxide content and temperature of the arterial blood[42].

b) Cardiopulmonary function determines the PaO_2, $PaCO_2$, and arterial pH. These values are established by alveolar minute ventilation[118] and the ventilation / perfusion ratio[119].

c) Cardiovascular function regulates the delivery of oxygenated blood to the tissues and this is determined by the interrelationship between cardiac output (i.e. blood flow), total peripheral resistance and systemic mean arterial blood pressure[37].

6.2.2 Etorphine

The results indicate that the administration of etorphine resulted in a gradual decrease in the oxygen consumption index, which reached a minimum value at 15 minutes PDA (Fig. 6.1). As a result, oxygen consumption index was significantly lower than the baseline value at 15 and 25 minutes PDA. During the subsequent 20 minutes, it gradually returned to the baseline value. The arterial and venous oxygen concentrations did not change significantly after the injection of the etorphine (Fig. 6.2 & 6.3). Despite a reduction in alveolar minute ventilation and an increase in physiologic shunt fraction, which resulted in a decrease in PaO_2, cardiopulmonary function maintained arterial oxygen concentration in the immobilized animals (Fig. 4.7, 4.8, 4.1& 6.2). Rather, the decrease in oxygen consumption index appears to have occurred as a result of a decrease in cardiac output (Fig. 5.3).

Subsequent to the administration of diprenorphine, the oxygen consumption index did not change significantly from the baseline value (Fig. 6.1). This reflected a return of the PaO_2, systemic mean arterial blood pressure, cardiac output, and arterial and venous oxygen concentrations to their respective baseline values (Fig. 4.1, 5.1, 5.2, 5.3, 6.2 & 6.3).

6.2.3 Etorphine / xylazine

The administration of etorphine / xylazine to the goats resulted in a rapid and significant decrease in the oxygen consumption index, which remained depressed until the diprenorphine was administered (Fig. 6.1). During this period the index remained significantly lower, when compared to the goats immobilized with etorphine, at 5 and 35 minutes PDA.

The administration of etorphine / xylazine resulted in a significant decrease in arterial oxygen concentration in the immobilized animals, whereas etorphine administered on its own, did not (Fig. 6.2). This difference, was due to a decrease in both arterial haemoglobin concentration and percentage oxygen saturation (Fig. 6.4 & 6.5). The decrease in haemoglobin concentration was probably related to the alpha$_2$-agonist activity of the xylazine. Xylazine binds to presynaptic alpha$_2$-adrenoceptors inhibiting the release of noradrenaline[61,110], which in turn reduces the stimulation of splenic alpha$_1$-adrenoceptors[74]. The splenic capsule relaxes, the spleen expands, resulting in increased storage of red blood cells[36].

The reduction in percentage oxygen saturation of the arterial blood appears to be due to a significant decrease in alveolar minute ventilation and increases in both physiologic shunt and physiologic dead space ventilation fractions (Fig. 6.5, 4.7, 4.8 & 4.9). The resulting decrease in PaO_2, was greater and remained so over a longer time period when compared to the reduction caused by the administration of etorphine on its own (Fig. 5.2.7). It is proposed that this greater reduction in PaO_2 was due to xylazine compounding the etorphine induced reduction in alveolar ventilation by increasing the resistance to airflow in the bronchi and / or reducing lung compliance[55,69]. Xylazine also appears to have increased the ventilation / perfusion mismatching

in the lungs[22,55,65]. Although not determined in this trial, the concurrent hypercapnia (Fig. 5.2.13) and acidosis (Fig. 5.2.14) would further reduce the percentage oxygen saturation of the arterial blood by shifting the oxygen-haemoglobin dissociation curve to the right[42].

It appears that changes to cardiovascular function induced by the administration of etorphine / xylazine, further contributed to the reduction in the oxygen consumption index. There was a reduction in cardiac output probably due to a direct depression of the myocardium by the xylazine (Fig. 5.3). As there was no significant change to total peripheral resistance, this resulted in a decrease in systemic mean arterial blood pressure and therefore a likely reduction in the supply of poorly oxygenated blood to the various tissues[94].

The administration of diprenorphine did not result in a significant change to the oxygen consumption index (Fig. 6.1). There was a temporary increase in arterial oxygen concentration, which reflected an improvement in arterial oxygen saturation, a persistent decrease in arterial haemoglobin concentration, and a temporary improvement in PaO_2 (Fig. 6.2, 6.5, 6.4 & 4.1). There was also a temporary improvement in systemic mean arterial blood pressure due to non-significant increases in both cardiac output and total peripheral resistance (Fig. 5.1, 5.3 & 5.2). The results indicate that there was a limited and temporary improvement in cardiopulmonary and cardiovascular function following the administration of diprenorphine. These improvements were possibly either as a result of diprenorphine antagonising the physiological effects of etorphine, an increase in activity of the goats immediately following the injection of diprenorphine or a combination of the two. What is apparent, is that the pharmacodynamic effects of xylazine prevented a significant improvement in the oxygen consumption index in the

goats. This is further supported by a significant increase in the oxygen consumption index following the administration of atipamezole (Fig. 6.1).

The return of the oxygen consumption index to the baseline value following the administration of atipamezole, was due to the variables used in its calculation, returning to their baseline values. The arterial oxygen concentration increased due to an increase in both arterial haemoglobin concentration and percentage arterial oxygen saturation (Fig. 6.2, 6.4 & 6.5). The oxygen saturation improved due to PaO_2 returning to the baseline value, as a result of an increase in alveolar minute ventilation and decreases in both physiologic shunt and physiologic dead space ventilation fractions (Fig. 4.1, 4.7, 4.8 & 4.9). The oxygen consumption index also increased as a result of improved cardiovascular function. The cardiac output and total peripheral resistance increased, re-establishing the baseline systemic mean arterial blood pressure (Fig. 5.3, 5.2 & 5.1). The reversal of the $alpha_2$-adrenoceptor effects of xylazine is expected to result in normal sympathetic tone to the cardiovascular system[52,109].

6.2.4 Etorphine / azaperone

The administration of etorphine / azaperone resulted in a gradual decrease in the oxygen consumption index which reached a minimum at 35 minutes PDA (Fig. 6.1). This value was significantly lower than the baseline value and lower than the index measured after etorphne. It was not significantly different from the minimum value resulting at 35 minutes PDA following the administration of etorphine / xylazine.

The gradual decrease in the oxygen consumption index in the immobilized goats was probably due to two main factors; an immediate and significant decrease in arterial oxygen concentration and a more gradual decrease in systemic mean arterial blood pressure (Fig. 6.2 & 5.1). The results indicate that the depressed arterial oxygen concentration, between 5 and 35 minutes PDA, was due to a combination of two factors. A gradual decrease in arterial haemoglobin concentration and an initial decrease in arterial oxygen saturation follow by a progressive recovery (Fig. 6.4 & 6.5). The decrease in haemoglobin concentration was likely due to direct antagonism of the $alpha_1$-receptors of the splenic capsule. Azaperone is reported to produce $alpha_1$-adrenoceptor blockade peripherally[91]. The changes in arterial oxygen saturation reflect the changes in PaO_2, an initial decrease follow by a progressive recovery (Fig. 4.1). As alveolar minute ventilation did not vary significantly during this period (5 to 35 minutes PDA), the recovery of PaO_2 after the initial decrease was probably due to a gradual decrease in the degree of ventilation / perfusion mismatching, as both percentage physiologic shunt and physiologic dead space ventilation decreased progressively during this time (Fig. 4.7, 4.8 & 4.9).

The gradual decrease in systemic mean arterial blood pressure was as a result of a gradual reduction in total peripheral resistance, most likely due to a progressive blockade of the $alpha_1$-receptors of peripheral blood vessels[52,91]. As there was no compensatory increase in cardiac output, blood pressure dropped (Fig. 5.3). The incremental decrease that followed, resulted in the delivery of poorly oxygenated blood to the body tissues and a progressive drop in the mean oxygen consumption index (Fig. 6.1).

The results indicate that the rapid and significant rise in the oxygen consumption index to above the baseline value following the administration of diprenorphine, was probably due to significant

increases in both arterial oxygen concentration and cardiac output to levels above their respective baseline values (Fig. 6.1, 6.2 & 5.3). The increase in arterial oxygen concentration was due to a significant increase in haemoglobin concentration above its baseline value, plus a return of percentage arterial oxygen saturation to its baseline value (Fig. 6.4 & 6.5). The rise in the haemoglobin concentration is not explained by the results of this trial, but appears to contradict the earlier proposal that the decrease in haemoglobin concentration between 5 and 35 minutes PDA was due to an $alpha_1$-adrenoceptor blockade by azaperone. Diprenorphine is an antagonist of the effects due to etorphine and does not apparently influence the effects of azaperone. An increase in activity of the goats possibly resulted in increased blood circulation, particularly of those areas where sludging of red blood cells occurred during the immobilization.

The decline in the oxygen consumption index, after its initial increase, from 45 to 75 minutes PDA was due to decreases in both arterial oxygen concentration and cardiac output during this period (Fig. 6.1, 6.2 & 5.3). The venous oxygen concentration did not change significantly (Fig. 6.3).

CHAPTER 7

GENERAL DISCUSSION AND CONCLUSIONS

Goats proved to be suitable animals in which to determine the physiological changes that occur in respiratory and cardiovascular function following the administration of etorphine, etorphine / xylazine and etorphine / azaperone. 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 felt that any adrenergic response in the goats prior to the administration of the immobilizing drugs was effectively minimized. Following each trial, the goats rapidly recovered without significant side effects.

The administration of etorphine to the goats resulted in respiratory depression similar to findings in various other immobilized animals species[43,104]. The decrease was due primarily to a slowing of respiratory rate, rather than a reduction in tidal volume. The addition of xylazine to the immobilizing drug treatment further compromised the respiratory function. The mechanism by which this occurred was not determined but possibly involved changes to lung compliance and / or increases in airway resistance. Respiratory function appeared to be further compromised by increases in ventilation / perfusion mismatching. The administration of etorphine / azaperone did not antagonise the respiratory depression due to etorphine, as has been reported by various authors[64,86]. However, respiratory function was not further compromised by the addition of azaperone.

The results of this trial suggest that etorphine increases sympathetic nervous system activity causing an increase in total peripheral resistance. There is also evidence to suggest that the decrease in cardiac output associated with this increase in total peripheral resistance may not be entirely due to a baroreceptor reflex. The etorphine may have a more direct effect including; receptor-mediated activation of the vagal-sympathetic system or a direct depressant action on the myocardium.

The administration of etorphine / xylazine did not result in a change to total peripheral resistance but did decrease cardiac output and thus systemic mean arterial blood pressure. Xylazine appears to blunt the pressor response due to etorphine by a mechanism as yet unknown. Possible mechanisms include the influence of hypoxia and hypercapnia on the peripheral vasculature. It may also occur as a result of central and / or peripheral activation of $alpha_2$-adrenoceptors. The results suggest that the decrease in cardiac output was due to a direct suppression of the myocardium by the xylazine.

Etorphine plus azaperone was shown not to affect cardiac output. However, the azaperone did appear to induce a decrease in total peripheral resistance, probably due to $alpha_1$-adrenoceptor blockade. These results agree with reports that the administration of azaperone with etorphine, as compared to etorphine on its own, results in lower blood pressures in elephant[48] and rhino[47].

Etorphine is reported to have variable effects on cardiovascular function depending on the animal species in which it is used and the other drugs with which it may be combined[44]. It was clearly demonstrated in this trial, that differences in cardiovascular function occurred due to the different drugs administered in combination with the etorphine.

The results of these trials indicate that all three immobilizing drug treatments adversely affected respiratory and cardiovascular function in immobilized goats. Etorphine / xylazine had the most negative effects, etorphine / azaperone less so and etorphine the least. Xylazine and azaperone are commonly used in combination with etorphine in the immobilization of free-ranging artiodactyls[44]. The rationale for their use includes; reduction of the dose of etorphine required, shorter induction times, improved muscle relaxation in the immobilized animal, reduced opioid induced excitement[13,86,87,104] and an apparent improved quality of the immobilization in wild animals. The results of this trial suggest that these benefits, have to be balanced against their negative pharmacodynamic effects on respiratory and cardiovascular function. This would seem to apply particularly to the use of etorphine / xylazine when compared to etorphine on it own or etorphine / azaperone.

The results indicate that in goats standing at rest all three immobilizing drug treatments reduced the oxygen consumption index, that is the supply of oxygenated blood to the tissues. The most significant and immediate decrease occurred following the administration of etorphine / xylazine. The decrease in oxygen consumption index was more progressive after the injection of etorphine / azaperone, however at 35 minutes PDA it had decreased to the same levels resulting from etorphine / xylazine. Etorphine had a very limited depressant effect. The results suggest that if etorphine is used in combination with a tranquillizer or a sedative, azaperone would be the drug of choice. It would allow the animal to remain immobilized for a longer period of time before the oxygen consumption index became severely depressed.

The results indicate that numerous physiological factors determine and regulate the oxygen consumption index. Therefore, the monitoring of heart rate, respiratory rate, respiratory depth

and on occasion oxygen saturation in the immobilized animal, is probably inadequate in determining the physiological status of the animal. The monitoring of other variables, e.g. blood pressures or partial pressures of blood gases, would be of great benefit, although not always practical in the field.

The effects the three immobilizing drug treatments had on respiratory and cardiovascular function, and oxygen consumption index were determined in animals standing at rest. What effects they may have in free-ranging animals, in which an adrenergic response and an increase in metabolic activity is frequently associated with a flight response due to the impact of the dart, requires investigation.

Diprenorphine proved to be effective in rapidly reversing the depressant effects of etorphine on respiratory and cardiovascular function. However, there was evidence to suggest that some residual respiratory depression persisted. Although, the blood gas partial pressures returned to baseline values following the administration of diprenorphine, the respiratory rate remained depressed.

Diprenorphine failed to effectively reverse the effects of etorphine / xylazine on respiratory and cardiovascular function. The results indicate that they were more effectively reversed once the atipamezole had been given. This indicates the need for both an opioid and an alpha$_2$-adrenoceptor antagonist to effectively antagonise the effects of etorphine plus xylazine. The results also suggested that although clinically an animal may appear fully recovered from the effects of immobilizing drugs, it may take longer for respiratory and cardiovascular functions to return to the steady state observed prior to administration of the immobilizing drugs.

Diprenorphine effectively antagonised the respiratory depression due to etorphine / azaperone, but caused little change to cardiovascular function.

SUMMARY

The physiological effects of etorphine, and etorphine combined with xylazine and etorphine combined with azaperone on respiratory and cardiovascular function were determined in Boer goats. The goats were habituated to the experimental procedures allowing the determination of respiratory and cardiovascular function while the animals stood quietly at rest. This resulted in the physiological changes induced by the three immobilizing drugs being measured and compared with those obtained prior to the administration of the immobilizing drugs. The effectiveness of diprenorphine and atipamezole in antagonising the physiological changes induced by the immobilizing drug treatments was also determined.

All three immobilizing drug treatments depressed respiratory function resulting in a decrease in PaO_2 and an increase in $PaCO_2$. Etorphine caused limited changes to these blood gases as a result of decreases in respiratory minute volume and alveolar minute ventilation caused by a fall in respiratory rate. The administration of etorphine / azaperone did not decrease the efficiency of respiration more significantly than when etorphine was administered on its own. Etorphine injected in combination with xylazine resulted in a severe decrease in respiratory function. The decrease in PaO_2 and the increase in $PaCO_2$ were much greater than the changes to these two blood gases following the administration of either etorphine or etorphine in combination with azaperone. Compared to etorphine administered on its own, etorphine combined with xylazine caused more significant decreases in tidal volume and alveolar minute ventilation, and more significant elevations in both physiological shunt fraction and percentage dead space ventilation.

The administration of etorphine, etorphine / xylazine and etorphine / azaperone caused three different sets of changes to cardiovascular function. The injection of etorphine resulted in

significant increases in both total peripheral resistance and systemic mean arterial blood pressure, and a significant decease in cardiac output. The administration of etorphine / xylazine resulted in a rapid and significant decrease in the systemic mean arterial blood pressure, followed by a decrease in cardiac output. The peripheral resistance remained unchanged. Etorphine / azaperone caused a progressive decline in the total peripheral resistance. As the cardiac output did not change significantly, the systemic mean arterial blood pressure fell progressively.

The administration of etorphine resulted in a gradual and limited decrease in the oxygen consumption index. Following the injection of etorphine / xylazine a rapid and significant decrease in the oxygen consumption index resulted, which was significantly lower, when compared to the goats immobilized with etorphine, at 5 and 35 minutes PDA. The injection of etorphine / azaperone resulted in a gradual decrease in the oxygen consumption index which reached a minimum value at 35 minutes PDA. At this time, the oxygen consumption index due to etorphine / xylazine was not significantly different from the value due to etorphine / azaperone.

Diprenorphine effectively reversed the respiratory and cardiovascular effects due to etorphine. The physiological changes induced by the administration of etorphine / xylazine were partially and temporarily antagonised by the administration of diprenorphine, it was only following the injection of atipamezole that they return to the values measured in the goats prior to immobilization. Diprenorphine effectively reversed the respiratory depression induced by etorphine / azaperone, however a mild acidosis persisted until the end of the trial period. The cardiac output and systemic mean blood pressure improved dramatically following the injection of diprenorphine but there was no immediate change in total peripheral resistance.

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APPENDIX A

RESPIRATORY FUNCTION : TABLES OF STATISTICAL PROBABILITIES

CONTENTS

ETORPHINE 137

PaO_2 137

$PaCO_2$ 137

Arterial pH 137

Respiratory minute volume 138

Respiratory rate 138

Tidal volume 138

Alveolar minute ventilation 139

Physiologic shunt fraction 139

Physiologic dead space ventilation fraction 139

ETORPHINE / XYLAZINE 140

PaO_2 140

$PaCO_2$ 140

Arterial pH 140

Respiratory minute volume 141

Respiratory rate 141

Tidal volume 141

Alveolar minute ventilation 142

Physiologic shunt fraction 142

Physiologic dead space ventilation fraction 142

ETORPHINE / AZAPERONE 143

PaO_2 143

$PaCO_2$ 143

Arterial pH 143

Respiratory minute volume 144

Respiratory rate 144

Tidal volume 144

Alveolar minute ventilation 144

Physiologic shunt fraction 145

Physiologic dead space ventilation fraction 145

COMPARISONS BETWEEN THE THREE TREATMENTS 146

PaO_2 146

$PaCO_2$ 147

Arterial pH 148

Respiratory minute volume 149

Respiratory rate 150

Tidal volume 151

Alveolar minute ventilation 152

Physiologic shunt fraction 153

Physiologic dead space ventilation fraction 154

APPENDIX A

RESPIRATORY FUNCTION

ETORPHINE

PaO_2 (mm Hg)

MBVR = 80.32	Difference	Probability
MBVR compared to 5 min PDA (66.38)	-13.94	0.046
5 min PDA compared to 35 min PDA (71.15)	4.77	0.9893
MBVR compared to 35 min PDA (71.15)	9.17	0.0079
35 min PDA compared to 45 min PDA (83.08)	11.93	0.0097
MBVR compared to 45 min PDA (83.08)	2.76	0.4951
MBVR compared to 95 min PDA (79.63)	-0.69	0.2413

$PaCO_2$ (mm Hg)

MBVR = 42.56	Difference	Probability
MBVR compared to 5 min PDA (47.04)	4.48	0.0386
5 min PDA compared to 35 min PDA (43.57)	-3.47	0.1834
MBVR compared to 35 min PDA (43.57)	1.01	0.5097
35 min PDA compared to 45 min PDA (43.30)	-0.27	0.6595
MBVR compared to 45 min PDA (43.30)	0.74	0.8072
MBVR compared to 95 min PDA (42.68)	0.12	0.9834

Arterial pH

MBVR = 7.398	Difference	Probability
MBVR compared to 5 min PDA (7.354)	-0.044	0.0075
5 min PDA compared to 35 min PDA (7.389)	0.035	0.0141
35 min PDA compared to 45 min PDA (7.384)	-0.005	0.7254
MBVR compared to 45 min PDA (7.384)	-0.014	0.1346
MBVR compared to 95 min PDA (7.397)	-0.001	0.9834

Respiratory minute volume (ml / minute)

MBVR = 12814.46	**Difference**	**Probability**
MBVR compared to 15 min PDA (6801.36)	-6013.1	0.0001
15 min PDA (6801.36) compared to 35 min PDA (8531.58)	1730.22	0.0204
35 min PDA compared to 45 min PDA (12378.07)	3846.49	0.1308
MBVR compared to 45 min PDA (12378.07)	-436.39	0.9246
MBVR compared to 65 min PDA (9029.36)	-3785.1	0.0344
MBVR compared to 95 min PDA (9980.58)	-2833.88	0.0167

Respiratory rate (breaths / minute)

MBVR = 36	**Difference**	**Probability**
MBVR compared to 5 min PDA (18)	-18	0.0004
15 min PDA (19) compared to 35 min PDA (21)	2	0.2321
35 min PDA compared to 45 min PDA (23)	2	0.4781
MBVR compared to 95 min PDA (22)	-14	0.0001

Tidal volume (ml / breath)

MBVR = 404.38	**Difference**	**Probability**
MBVR compared to 5 min PDA (444.88)	40.5	0.422
15 min PDA (393.01) compared to 35 min PDA (436.18)	43.17	0.2928
35 min PDA compared to 45 min PDA (503.44)	67.26	0.539
MBVR compared to 95 min PDA (493.52)	89.14	0.0863

Alveolar minute ventilation (ml / minute)

MBVR = 3783.81	**Difference**	**Probability**
MBVR compared to 15 min PDA (2549.86)	-1233.95	0.0005
15 min PDA compared to 35 min PDA (3269.57)	719.71	0.0191
35 min PDA compared to 45 min PDA (3870.80)	601.23	0.8194
MBVR compared to 45 min PDA (3870.80)	86.99	0.817
MBVR compared to 65 min PDA (3216.09)	-567.72	0.1205
MBVR compared to 75 min PDA (3316.09)	-467.44	0.1891
MBVR compared to 95 min PDA (3956.10)	172.29	0.9444

Physiologic shunt fraction (%)

MBVR = 11.02	**Difference**	**Probability**
MBVR compared to 5 min PDA (22.41)	11.39	0.2416
35 min PDA (15.96) compared to 45 min PDA (12.84)	3.12	0.8001
MBVR compared to 45 min PDA (12.84)	1.82	0.6211
MBVR compared to 95 min PDA (13.05)	2.03	0.68

Physiologic dead space ventilation fraction (%)

MBVR = 62.80	**Difference**	**Probability**
MBVR compared to 5 min PDA (57.88)	-4.92	0.0001
35 min PDA (57.02) compared to 45 min PDA (60.18)	3.16	0.3713
MBVR compared to 45 min PDA (60.18)	-2.62	0.0001
MBVR compared to 95 min PDA (55.96)	-6.84	0.0001

ETORPHINE / XYLAZINE

PaO_2 (mm Hg)

MBVR = 81.53	Difference	Probability
MBVR compared to 5 min PDA (43.15)	-38.38	0.0001
5 min PDA compared to 35 min PDA (52.00)	8.85	0.0618
35 min PDA compared to 45 min PDA (69.17)	17.17	0.0018
MBVR compared to 45 min PDA (69.17)	-12.36	0.0151
65 min PDA (58.63 mmHg) compared to 75 min PDA (78.75)	-20.12	0.0001
MBVR compared to 75 min PDA (78.75)	-2.78	0.2397
MBVR compared to 95 min PDA (74.55)	-6.98	0.0001

$PaCO_2$ (mm Hg)

MBVR = 40.62	Difference	Probability
MBVR compared to 5 min PDA (55.18)	14.56	0.0001
5 min PDA compared to35 min PDA(56.83)	1.65	0.4389
35 min PDA compared to 45 min PDA (51.18)	-5.56	0.0382
MBVR compared to 45 min PDA (51.18)	10.56	0.0001
65 min PDA (53.93 mmHg) compared to 75 min PDA (44.87)	-9.06	0.0001
MBVR compared to 75 min PDA (44.87)	4.25	0.0001
MBVR compared to 95 min PDA (44.97)	4.35	0.0039

Arterial pH

MBVR = 7.396	Difference	Probability
MBVR compared to 5 min PDA (7.298)	-0.098	0.0001
5 min p.d.a .compared to 35 min PDA (7.306)	0.008	0.3304
35 min PDA compared to 45 min PDA (7.348)	0.042	0.0048
MBVR compared to 45 min PDA (7.348)	-0.048	0.0001
65 min PDA (7.334) compared to 75 min PDA (7.372)	0.038	0.0031
MBVR compared to 75 min PDA (7.372)	-0.024	0.0027
MBVR compared to 95 min PDA (7.383)	-0.013	0.1402

Respiratory minute volume (ml / minute)

MBVR = 12406.91	Difference	Probability
MBVR compared to 5 min PDA (5955.26)	-6451.65	0.0004
5 min PDA compared to 35 min PDA (5208.55)	-746.71	0.4577
35 min PDA compared to 45 min PDA (9798.16)	4589.61	0.0701
MBVR compared to 45 min PDA (9798.16)	-2608.75	0.3058
MBVR compared to 65 min PDA (5052.40)	-7354.51	0.0002
65 min PDA compared to 75 min PDA (10702.67)	5650.27	0.0019
MBVR compared to 75 min PDA (10702.67)	-1704.24	0.1048
MBVR compared to 95 min PDA (7629.36)	-4777.55	0.0004

Respiratory rate (breaths / minute)

MBVR = 37	Difference	Probability
MBVR compared to 5 min PDA (19)	-18	0.0003
5 min PDA compared to 35 min PDA (21)	-2	0.465
35 min PDA compared to 45 min PDA (27)	6	0.3292
MBVR compared to 65 min PDA (23)	-14	0.0106
65 min PDA compared to 75 min PDA (19)	-4	0.3824
MBVR compared to 95 min PDA (17)	-20	0.0001

Tidal volume (ml / breath)

MBVR = 402.28	Difference	Probability
MBVR compared to 5 min PDA (328.65)	-73.63	0.1285
5 min PDA compared to 35 min PDA (299.00)	-29.65	0.6319
MBVR compared to 35 min PDA (299.00)	-103.28	0.0296
35 min PDA compared to 45 min PDA (379.00)	80.29	0.2608
MBVR compared to 65 min PDA (274.56)	-127.72	0.0339
65 min PDA compared to 75 min PDA (570.94)	296.38	0.0001
MBVR compared to 95 min PDA (462.89)	60.61	0.2314

Alveolar minute ventilation (ml / minute)

MBVR = 4260.89	Difference	Probability
MBVR compared to 5 min PDA (1882.67)	-2378.22	0.0002
5 min PDA compared to 35 min PDA (1575.09)	-307.58	0.435
35 min PDA compared to 45 min PDA (1194.79)	1194.79	0.2193
MBVR compared to 45 min PDA (279.88)	-1491.01	0.2715
MBVR compared to 65 min PDA (1455.42)	-2805.47	0.0004
65 min PDA compared to 75 min PDA (4399.61)	2944.19	0.0001
MBVR compared to 75 min PDA (4399.61)	138.72	0.6149
MBVR compared to 95 min PDA (3027.18)	-1233.71	0.01

Physiologic shunt fraction (%)

MBVR = 13.36	Difference	Probability
MBVR compared to 5 min PDA (53.52)	40.16	0.0001
MBVR compared to 35 min PDA (46.01)	32.65	0.0001
35 min PDA compared to 45 min PDA (25.59)	20.42	0.0011
MBVR compared to 45 min PDA (25.59)	12.23	0.0215
MBVR compared to 65 min PDA (42.21)	28.85	0.0023
65 min PDA compared to 75 min PDA (15.16)	27.05	0.0042
MBVR compared to 75 min PDA (15.16)	1.8	0.3148
MBVR compared to 95 min PDA (19.57)	6.21	0.065

Physiologic dead space ventilation fraction (%)

MBVR = 62.48	Difference	Probability
MBVR compared to 15 min PDA (67.69)	5.21	0.0094
MBVR compared to 35 min PDA (66.41)	3.93	0.0025
35 min PDA compared to 45 min PDA (67.04)	0.63	0.8351
MBVR compared to 45 min PDA (67.04)	4.56	0.0001
MBVR compared to 65 min PDA (69.79)	7.31	0.0151
65 min PDA compared to 75 min PDA (55.57)	-14.22	0.0001
MBVR compared to 95 min PDA (56.14)	-6.34	0.0001

ETORPHINE / AZAPERONE

PaO_2 (mm Hg)

MBVR = 79.70	Difference	Probability
MBVR compared to 5 min PDA (55.70)	-24	0.0009
5 min PDA compared to 35 min PDA (67.98)	12.28	0.0898
35 min PDA compared to 45 min PDA (78.87)	10.89	0.0133
MBVR compared to 45 min PDA (78.87)	-0.83	0.8156
MBVR compared to 75 min PDA (79.78)	0.08	0.9097

$PaCO_2$ (mm Hg)

MBVR = 41.12	Difference	Probability
MBVR compared to 5 min PDA (47.42)	6.3	0.0012
5 min PDA compared to 35 min (47.10)	-0.32	0.7288
35 min PDA compared to 45 min PDA (43.55)	-3.55	0.1456
MBVR compared to 45 min PDA (43.55)	2.43	0.0936
MBVR compared to 75 min PDA (41.35)	0.23	0.8301

Arterial pH

MBVR = 7.402	Difference	Probability
MBVR compared to 5 min PDA (7.338)	-0.064	0.0001
15 min PDA compared to 35 min PDA (7.346)	0.016	0.0153
35 min PDA compared to 45 min PDA (7.343)	-0.003	0.9224
MBVR compared to 75 min PDA (7.355)	0.047	0.0001

Respiratory minute volume (ml / minute)

MBVR = 12575.79	Difference	Probability
MBVR compared to 5 min PDA (6194.00)	-6381.79	0.0005
5 min PDA compared to 35 min PDA (7152.56)	958.56	0.3568
35 min PDA compared to 45 min PDA (16567.10)	9414.54	0.011
MBVR compared to 45 min PDA (16567.10)	3991.31	0.1503
MBVR compared to 75 min PDA (11397.66)	-1178.13	0.7375

Respiratory rate (breaths / minute)

MBVR = 32	Difference	Probability
MBVR compared to 5 min PDA (15)	-17	0.0001
15 min PDA compared to 35 min p.d.a (23).	8	0.0049
35 min PDA compared to 45 min PDA (26)	3	0.4471
MBVR compared to 75 min PDA (25)	-8	0.0001

Tidal volume (ml / breath)

MBVR = 444.10	Difference	Probability
MBVR compared to 15 min PDA (309.40)	-134.7	0.041
15 min PDA compared to 35 min PDA (352.71)	43.31	0.387
35 min PDA compared to 45 min PDA (614.25)	261.54	0.001
MBVR compared to 75 min PDA (468.40)	24.3	0.5021

Alveolar minute ventilation (ml / minute)

MBVR = 4354.97	Difference	Probability
MBVR compared to 5 min PDA (2203.98)	2150.99	0.0006
5 min PDAcompared to 35 min p.d. a. (2505.00)	301.02	0.4207
35 min PDA compared to 45 min PDA (6470.64)	3965.64	0.0011
MBVR compared to 45 min PDA (6470.64)	-2115.67	0.0366
MBVR compared to 75 min PDA (4323.29)	-31.68	0.2897

Physiologic shunt fraction (%)

MBVR = 12.73	**Difference**	**Probability**
MBVR compared to 5 min PDA (40.70)	27.97	0.0025
MBVR compared to 35 min PDA (28.68)	15.95	0.0031
35 min PDA compared to 45 min PDA (17.87)	10.81	0.049
MBVR compared to 45 min PDA (17.87)	5.14	0.2925
MBVR compared to 75 min PDA (17.87)	5.14	0.0328

Physiologic dead space ventilation fraction (%)

MBVR = 62.81	**Difference**	**Probability**
MBVR compared to 5 min PDA (58.96)	3.85	0.0108
MBVR compared to 35 min PDA (60.35)	2.46	0.0001
35 min PDA compared to 45 min PDA (57.61)	2.74	0.4242
MBVR compared to 45 min PDA (57.61)	5.2	0.0001
MBVR compared to 75 min PDA (58.50)	4.31	0.0001

COMPARISONS BETWEEN THE THREE TREATMENTS

PaO_2 (mm Hg)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-13.94	-38.38	24.44	0.0082
5 min PDA	66.38	43.15	23.23	0.0012
15 min PDA	69.92	48.92	21	0.0098
25 min PDA	71.38	49.35	22.03	0.0006
35 min PDA	71.15	52	19.15	0.0092
35 min PDA compared to 45 min PDA	11.93	17.17	5.24	0.5354
45min PDA	83.08	69.17	13.91	0.0543

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-13.94	-24	10.06	0.1664
5 min PDA	66.38	55.7	10.68	0.3674
15 min PDA	69.92	62.65	7.27	0.1847
25 min PDA	71.38	66.34	5.04	0.2159
35 min PDA	71.15	67.98	3.17	0.1205
35 min PDA compared to 45 min PDA	11.93	10.89	1.04	0.9292
45min PDA	83.08	78.87	4.21	0.6336

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-38.38	-24	14.38	0.1035
5 min PDA	43.15	55.7	12.55	0.0028
15 min PDA	48.92	62.65	13.73	0.0058
25 min PDA	49.35	66.34	16.99	0.0033
35 min PDA	52	67.98	15.98	0.0016
35 min PDA compared to 45 min PDA	17.17	10.89	6.28	0.4774
45min PDA	69.17	78.87	9.7	0.1084

$PaCO_2$ (mmHg)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	4.48	14.56	10.08	0.0008
5 min PDA	47.04	55.18	8.14	0.0012
15 min PDA	46.28	56.53	10.25	0.0008
25 min PDA	45.7	58.43	12.73	0.0006
35 min PDA	43.57	56.83	13.26	0.0002
35 min PDA compared to 45 min PDA	-0.27	-5.65	5.38	0.2439
45min PDA	43.3	51.18	7.88	0.0004

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	4.48	6.3	1.82	0.3543
5 min PDA	47.04	47.42	0.38	0.3674
15 min PDA	46.28	48.43	2.15	0.1847
25 min PDA	45.7	48.67	2.97	0.2159
35 min PDA	43.57	47.1	3.53	0.1205
35 min PDA compared to 45 min PDA	-0.27	-3.55	3.28	0.4857
45min PDA	43.3	43.55	0.25	0.3334

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	14.56	6.3	8.26	0.002
5 min PDA	55.18	47.42	7.76	0.0028
15 min PDA	56.53	48.43	8.1	0.0058
25 min PDA	58.43	48.67	9.76	0.0038
35 min PDA	56.83	47.1	9.73	0.0016
35 min PDA compared to 45 min PDA	-5.65	-3.55	2.1	0.5737
45min PDA	51.18	43.55	7.63	0.0014

Arterial pH

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-0.044	-0.098	0.054	0.0016
5 min PDA	7.354	7.298	0.056	0.0009
15 min PDA	7.362	7.298	0.064	0.0034
25 min PDA	7.376	7.302	0.074	0.0009
35 min PDA	7.389	7.306	0.083	0.0004
35 min PDA compared to 45 min PDA	0.005	0.042	0.037	0.02
45min PDA	7.384	7.348	0.036	0.0061

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.044	-0.064	0.02	0.1135
5 min PDA	7.354	7.338	0.016	0.097
15 min PDA	7.362	7.33	0.032	0.0573
25 min PDA	7.376	7.338	0.038	0.0281
35 min PDA	7.389	7.346	0.043	0.0265
35 min PDA compared to 45 min PDA	0.005	0.003	0.002	0.8578
45min PDA	7.384	7.343	0.041	0.0022

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.098	-0.064	0.034	0.0347
5 min PDA	7.298	7.338	0.04	0.0181
15 min PDA	7.298	7.33	0.032	0.1592
25 min PDA	7.302	7.338	0.036	0.089
35 min PDA	7.306	7.346	0.04	0.0447
35 min PDA compared to 45 min PDA	0.042	0.003	0.039	0.0292
45min PDA	7.348	7.343	0.005	0.6111

Respiratory minute volume (ml / minute)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-4760.89	-6451.65	1690.76	0.3277
5 min PDA	8053.57	5955.26	2098.31	0.2691
15 min PDA	6801.36	5384.89	1416.47	0.2185
25 min PDA	8158.51	5787.5	2371.01	0.16
35 min PDA	8531.58	5208.55	3323.03	0.0488
35 min PDA compared to 45 min PDA	3846.49	4589.61	743.12	0.805
45min PDA	12378.07	9798.16	2579.91	0.5872

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-4760.89	-6381.79	1620.9	0.3838
5 min PDA	8053.57	6194	1859.57	0.3173
15 min PDA	6801.36	6682.47	118.89	0.6854
25 min PDA	8158.51	6381.44	1777.07	0.2704
35 min PDA	8531.58	7152.56	1379.02	0.3172
35 min PDA compared to 45 min PDA	3846.49	9414.54	5568.05	0.1146
45min PDA	12378.07	16567.1	4189.03	0.2934

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-6451.65	-6381.79	69.86	0.905
5 min PDA	5955.26	6194	238.74	0.857
15 min PDA	5384.89	6682.47	1297.58	0.3544
25 min PDA	5787.5	6381.44	593.94	0.6918
35 min PDA	5208.55	7152.56	1944.01	0.231
35 min PDA compared to 45 min PDA	4589.61	9414.54	4824.93	0.1744
45min PDA	9798.16	16567.1	6768.94	0.1057

Respiratory rate (breaths / minute)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-18	-18	0	0.8067
5 min PDA	18	19	1	0.9703
15 min PDA	19	19	0	0.6868
25 min PDA	20	20	0	0.8677
35 min PDA	21	21	0	0.8996
35 min PDA compared to 45 min PDA	2	6	4	0.8983
45min PDA	23	27	4	0.6015

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-18	-17	1	0.521
5 min PDA	18	15	3	0.4743
15 min PDA	19	22	3	0.6437
25 min PDA	20	21	1	0.9765
35 min PDA	21	23	2	0.7938
35 min PDA compared to 45 min PDA	2	3	1	0.9767
45min PDA	23	26	3	0.6759

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-18	-17	1	0.3572
5 min PDA	19	15	4	0.4893
15 min PDA	19	22	3	0.3818
25 min PDA	20	21	1	0.834
35 min PDA	21	23	2	0.6976
35 min PDA compared to 45 min PDA	6	3	3	0.8634
45min PDA	27	26	1	0.3545

Tidal volume (ml / breath)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-40.5	-73.63	33.13	0.1112
5 min PDA	444.88	328.65	116.23	0.1413
15 min PDA	393.01	311.01	82	0.2535
25 min PDA	432.71	333.9	98.81	0.0703
35 min PDA	436.18	299	137.18	0.0143
35 min PDA compared to 45 min PDA	-67.26	80.29	13.03	0.7471
45min PDA	503.44	379.29	124.15	0.4617

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-40.5	-21.68	18.82	0.965
5 min PDA	444.88	465.78	20.9	0.8809
15 min PDA	393.01	309.4	83.61	0.1952
25 min PDA	432.71	328.01	104.7	0.0419
35 min PDA	436.18	352.71	83.47	0.0438
35 min PDA compared to 45 min PDA	67.26	261.54	194.28	0.0318
45min PDA	503.44	614.25	110.81	0.1254

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-73.63	-21.68	51.95	0.1068
5 min PDA	328.65	465.78	137.13	0.1151
15 min PDA	311.01	309.4	1.61	0.9286
25 min PDA	333.9	328.01	5.89	0.8798
35 min PDA	299	352.71	53.71	0.4139
35 min PDA compared to 45 min PDA	89.29	261.54	181.25	0.05
45min PDA	379.29	614.25	234.96	0.0164

Alveolar minute ventilation (ml / minute)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-799.72	-2378.22	1578.5	0.095
5 min PDA	2984.09	1882.67	1101.42	0.0885
15 min PDA	2549.86	1529.48	1020.38	0.0292
25 min PDA	3018.14	1699	1319.14	0.0171
35 min PDA	3269.57	1575.09	1694.48	0.0047
35 min PDA compared to 45 min PDA	601.23	1194.79	593.56	0.5179
45min PDA	3870.8	2769.88	1100.92	0.6938

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-799.72	-2150.99	1351.27	0.2052
5 min PDA	2984.09	2203.98	780.11	0.2529
15 min PDA	2549.86	2221.01	328.85	0.8151
25 min PDA	3018.14	2198.9	819.24	0.2193
35 min PDA	3269.57	2505	764.57	0.2373
35 min PDA compared to 45 min PDA	601.23	3965.64	3364.41	0.0252
45min PDA	3870.8	6470.64	2599.84	0.0533

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-2378.22	-2150.99	227.23	0.6416
5 min PDA	1882.67	2203.98	321.31	0.5246
15 min PDA	1529.48	2221.01	691.53	0.0501
25 min PDA	1699	2198.9	499.9	0.1922
35 min PDA	1575.09	2505	929.91	0.0574
35 min PDA compared to 45 min PDA	1194.79	3965.64	2770.85	0.0561
45min PDA	2769.88	6470.64	3700.76	0.0137

Physiologic shunt fraction (%)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	11.39	40.16	28.77	0.0096
5 min PDA	22.41	53.52	31.11	0.0141
15 min PDA	21.35	48.35	27	0.0016
25 min PDA	19.01	44.93	25.92	0.0003
35 min PDA	15.96	46.01	30.05	0.0008
35 min PDA compared to 45 min PDA	-3.12	-20.42	17.3	0.0184
45min PDA	12.84	25.59	12.75	0.0681

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	11.39	27.97	16.58	0.1055
5 min PDA	22.41	40.7	18.29	0.1249
15 min PDA	21.35	31.43	10.08	0.2527
25 min PDA	19.01	30.29	11.28	0.0596
35 min PDA	15.96	28.68	12.72	0.1046
35 min PDA compared to 45 min PDA	-3.12	-10.81	7.69	0.2073
45min PDA	12.84	17.87	5.03	0.9516

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	40.16	27.97	12.19	0.2282
5 min PDA	53.52	40.7	12.82	0.2305
15 min PDA	48.35	31.43	16.92	0.0184
25 min PDA	44.93	30.29	14.64	0.0137
35 min PDA	46.01	28.68	17.33	0.0248
35 min PDA compared to 45 min PDA	-20.42	-10.81	9.61	0.1868
45min PDA	25.59	17.87	7.72	0.0875

Physiologic dead space ventilation fraction (%)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-4.92	2.45	2.47	0.0091
5 min PDA	57.88	64.93	7.05	0.1611
15 min PDA	59.55	67.69	8.14	0.0224
25 min PDA	56.93	65.56	8.63	0.0231
35 min PDA	57.02	66.41	9.39	0.027
35 min PDA compared to 45 min PDA	3.16	0.63	2.53	0.6227
45min PDA	60.18	67.04	6.86	0.0155

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-4.92	-3.85	1.07	0.1094
5 min PDA	57.88	58.96	1.08	0.8773
15 min PDA	59.55	61.33	1.78	0.4011
25 min PDA	56.93	60.06	3.13	0.2895
35 min PDA	57.02	60.35	3.33	0.3206
35 min PDA compared to 45 min PDA	3.16	-2.74	0.42	0.2371
45min PDA	60.18	57.61	2.57	0.4013

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	2.45	-3.85	1.4	0.2235
5 min PDA	64.93	58.96	5.97	0.1783
15 min PDA	67.69	61.33	6.36	0.1083
25 min PDA	65.56	60.06	5.5	0.1656
35 min PDA	66.41	60.35	6.06	0.1684
35 min PDA compared to 45 min PDA	0.63	-2.74	2.11	0.4763
45min PDA	67.04	57.61	9.43	0.0028

APPENDIX B

CARDIOVASCULAR FUNCTION : TABLES OF STATISTICAL PROBABILITIES

CONTENTS

ETORPHINE 157

Systemic mean arterial blood pressure 157

Total peripheral resistance 157

Cardiac output 157

Heart rate 158

Stroke volume 158

ETORPHINE / XYLAZINE 159

Systemic mean arterial blood pressure 159

Total peripheral resistance 159

Cardiac output 159

Heart rate 160

Stroke volume 160

ETORPHINE / AZAPERONE 161

Systemic mean arterial blood pressure 161

Total peripheral resistance 161

Total peripheral resistance 161

Cardiac output 161

Heart rate 162

Stroke volume 162

COMPARISONS BETWEEN THE THREE TREATMENTS 163

Systemic mean arterial blood pressure 163

Total peripheral resistance 164

Cardiac output 165

Heart rate 166

Stroke volume 167

APPENDIX B

CARDIOVASCULAR FUNCTION

ETORPHINE

Systemic mean arterial blood pressure (mm Hg)

MBVR = 115.00	Difference	Probability
MBVR compared to 15 min PDA (139.50)	24.5	0.0134
15 min p.d.a compared to 35 min PDA (130.00)	-9.5	0.1872
35 min PDA compared to 45 min PDA (127.67)	-2.33	0.6127
MBVR compared to 55 min PDA (113.67)	-1.33	0.4671
MBVR compared to 95 min PDA (106.33)	-8.67	0.1532

Total peripheral resistance (P R U)

MBVR = 1.23	Difference	Probability
MBVR compared to 5 min PDA (1.84)	0.61	0.0001
5 min p.d.a compared to 35 min PDA (1.69)	-0.15	0.2218
35 min PDA compared to 45 min PDA (1.26)	-0.43	0.0033
MBVR compared to 45 min PDA (1.26)	0.03	0.5053
MBVR compared to 95 min PDA (1.14)	-0.09	0.4317

Cardiac output (L / minute)

MBVR = 5.77	Difference	Probability
MBVR compared to 5 min PDA (4.26)	-1.51	0.0057
5 min p.d.a compared to 35 min PDA (4.69)	0.43	0.2727
35 min PDA compared to 45 min PDA (6.14)	1.45	0.0001
MBVR compared to 45 min PDA (6.14)	0.37	0.2793
MBVR compared to 95 min PDA (5.71)	0.06	0.3167

Heart rate (beats / minute)

MBVR = 77.24	**Difference**	**Probability**
MBVR compared to 5 min PDA (58.19)	-19.05	0.0001
5 min p.d.a compared to 35 min PDA (63.80)	5.61	0.3112
35 min PDA compared to 45 min PDA (98.29)	34.49	0.0009
MBVR compared to 45 min PDA (98.29)	21.05	0.0158
MBVR compared to 95 min p.d.a . (85.62)	8.38	0.0788

Stroke volume (ml / beat)

MBVR = 74.97	**Difference**	**Probability**
MBVR compared to 5 min PDA (74.17)	-0.8	0.9173
5 min p.d.a compared to 35 min PDA (73.45)	-0.72	0.7535
35 min PDA compared to 45 min PDA (64.93)	-8.52	0.0214
MBVR compared to 45 min PDA (64.93)	-10.04	0.0824
MBVR compared to 95 min PDA (68.59)	-6.38	0.2384

ETORPHINE / XYLAZINE

Systemic mean arterial blood pressure (mm Hg)

MBVR = 115.78	Difference	Probability
MBVR compared to 5 min PDA (81.83)	-33.95	0.0001
5 min p.d.a compared to 35 min PDA (75.83)	-6	0.4672
35 min PDA compared to 45 min PDA (93.50)	17.67	0.0241
MBVR compared to 45 min PDA (93.50)	-22.28	0.0005
65 min p.d.a compared to 75 min PDA (135.5)	48.33	0.0001
MBVR compared to 95 min PDA (118.17)	2.39	0.6404

Total peripheral resistance (PRU)

MBVR = 1.12	Difference	Probability
MBVR compared to 5 min PDA (1.04)	-0.08	0.1572
5 min p.d.a compared to 35 min PDA (0.99)	-0.05	0.9101
35 min PDA compared to 45 min PDA (1.13)	0.14	0.2923
MBVR compared to 45 min PDA (1.13)	0.01	0.5585
65 min PDA (1.01) compared to 75 min PDA (1.39)	0.38	0.0001
MBVR compared to 95 min PDA (1.41)	0.29	0.0134

Cardiac output (L / minute)

MBVR = 6.24	Difference	Probability
MBVR compared to 5 min PDA (5.21)	-1.03	0.0696
5 min p.d.a compared to 35 min PDA (5.07)	-0.14	0.7122
MBVR compared to 35 min PDA (5.07)	-1.17	0.0148
35 min PDA compared to 45 min PDA (5.12)	0.05	0.9811
MBVR compared to 45 min PDA (5.12)	-1.12	0.0042
MBVR compared to 65 min PDA (5.28)	-0.96	0.0352
65 min p.d.a compared to 75 min PDA (5.85)	0.57	0.0794
MBVR compared to 75 min PDA (5.85)	0.39	0.6665
MBVR compared to 95 min PDA (5.06)	-1.18	0.0015

Heart rate (beats / minute)

MBVR = 80.00	**Difference**	**Probability**
MBVR compared to 5 min PDA (75.80)	-4.2	0.2544
5 min p.d.a compared to 35 min PDA (78.10)	2.3	0.6095
35 min PDA compared to 45 min PDA (72.85)	-5.25	0.5346
65 min p.d.a (77.78) compared to 75 min PDA (89.65)	11.87	0.0372
MBVR compared to 95 min PDA (73.61)	-6.39	0.1639

Stroke volume (ml / beat)

MBVR = 79.13	**Difference**	**Probability**
MBVR compared to 5 min PDA (71.01)	-8.12	0.1241
5 min PDA compared to 35 min PDA (64.70)	-6.31	0.3676
35 min PDA compared to 45 min PDA (71.52)	-6.82	0.0545
MBVR compared to 45 min PDA (71.52)	-7.61	0.3676
75 min PDA (67.93) compared to 85 min PDA (72.96)	5.03	0.1007
MBVR compared to 95 min PDA (71.34)	-7.79	0.1968

ETORPHINE / AZAPERONE

Systemic mean arterial blood pressure (mm Hg)

MBVR = 118.94	Difference	Probability
MBVR compared to 15 min PDA (90.17)	-28.77	0.0052
15 min PDA compared to 35 minPDA (84.50)	-5.67	0.4888
35 min p.d.a compared to 45 min PDA (110.83)	26.33	0.001
MBVR compared to 45 min PDA (110.83)	-8.11	0.2776
MBVR compared to 75 min p.d.a (108.67)	-10.27	0.1928

Total peripheral resistance (PRU)

MBVR = 1.25	Difference	Probability
MBVR compared to 5 min PDA (0.99)	-0.26	0.088
5 min PDA compared to 35 min PDA (0.82)	-0.17	0.1529
MBVR compared to 35 min PDA (0.82)	-0.43	0.0193
35 min PDA compared to 45 min PDA (0.73)	-0.09	0.4853
MBVR compared to 55 min PDA (0.72)	-0.53	0.0001
MBVR compared to 75 min PDA (0.88)	-0.37	0.0001

Cardiac output (L / minute)

MBVR = 5.83	Difference	Probability
MBVR compared to 5 min PDA (6.57)	7.4	0.1599
5 min p.d.a compared to 35 min PDA (6.28)	-0.29	0.4621
35 min PDA compared to 45 min PDA (9.22)	2.94	0.0001
MBVR compared to 45 min PDA (9.22)	3.39	0.0001
MBVR compared to 75 min p.d.a (7.5)	1.67	0.0003

Heart rate (beats / minute)

MBVR = 81.33	**Difference**	**Probability**
MBVR compared to 5 min PDA (78.84)	-2.49	0.5311
5 min p.d.a compared to 35 min PDA (88.77)	9.93	0.0419
35 min PDA compared to 45 min PDA (144.45)	55.68	0.0001
MBVR compared to 45 min PDA (144.45)	63.12	0.0001
MBVR compared to 75 min PDA (118.92)	37.59	0.0001

Stroke volume (ml / beat)

MBVR = 73.36	**Difference**	**Probability**
MBVR compared to 5 min PDA (85.61)	1225	0.0339
5 min PDA compared to 15 min PDA (71.72)	-13.89	0.0012
MBVR compared to 15 min PDA (71.72)	-1.64	0.6171
35 min PDA (70.84) compared to 45 min PDA (64.42)	-6.42	0.0699
MBVR compared to 55 min PDA (71.49)	-1.87	0.4198
MBVR compared to 75 min PDA (63.15)	-10.21	0.0055

COMPARISONS BETWEEN THE THREE TREATMENTS

Systemic mean arterial blood pressure (mm Hg)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	15	-33.95	18.95	0.0001
5 min PDA	130	81.83	48.17	0.0002
15 min PDA	139.5	84.5	55	0.0007
25 min PDA	127.17	82.67	44.5	0.0036
35 min PDA	130	75.83	54.17	0.0001
35 min PDA compared to 45 min PDA	-2.33	17.67	15.34	0.0489
45min PDA	127.67	93.5	34.17	0.0005

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	15	-12.44	2.56	0.0194
5 min PDA	130	106.5	23.5	0.0216
15 min PDA	139.5	90.17	49.33	0.0009
25 min PDA	127.17	85.65	41.52	0.0036
35 min PDA	130	84.5	45.5	0.0001
35 min PDA compared to 45 min PDA	-2.33	26.33	24	0.0055
45min PDA	127.67	110.83	16.84	0.0005

c) Etorphine / xylazine compared to etorphine / azaperone

MBVR	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-33.95	-12.44	21.51	0.0237
5 min PDA	81.83	106.5	25.17	0.0427
15 min PDA	84.5	90.17	5.67	0.9875
25 min PDA	82.67	85.65	2.98	0.9355
35 min PDA	75.83	84.5	8.67	0.4228
35 min PDA compared to 45 min PDA	17.67	26.33	8.66	0.2707
45min PDA	93.5	110.83	17.33	0.049

Total peripheral resistance (PRU)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	0.61	-0.08	0.53	0.0002
5 min PDA	1.84	1.04	0.8	0.0007
15 min PDA	1.7	1.05	0.65	0.0317
25 min PDA	1.62	1.07	0.55	0.1245
35 min PDA	1.69	0.99	0.7	0.0043
35 min PDA compared to 45 min PDA	-0.43	0.14	0.29	0.0063
45min PDA	1.26	1.13	0.13	0.3531

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	0.61	-0.26	0.35	0.0001
5 min PDA	1.84	0.99	0.85	0.0002
15 min PDA	1.7	0.98	0.72	0.0063
25 min PDA	1.62	0.91	0.71	0.0246
35 min PDA	1.69	0.82	0.87	0.0006
35 min PDA compared to 45 min PDA	-0.43	-0.09	0.34	0.0663
45min PDA	1.26	0.73	0.53	0.0003

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.08	-0.26	0.18	0.8341
5 min PDA	1.04	0.99	0.05	0.8033
15 min PDA	1.05	0.98	0.07	0.5887
25 min PDA	1.07	0.91	0.16	0.51
35 min PDA	0.99	0.82	0.17	0.5579
35 min PDA compared to 45 min PDA	0.14	-0.09	0.05	0.2293
45min PDA	1.13	0.73	0.4	0.004

Cardiac output (L / minute)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-1.51	-1.03	0.48	0.3937
5 min PDA	4.26	5.21	0.95	0.333
15 min PDA	4.97	5.43	0.46	0.9167
25 min PDA	4.86	5.39	0.53	0.8754
35 min PDA	4.69	5.07	0.38	0.9549
35 min PDA compared to 45 min PDA	1.45	0.05	1.4	0.0013
45min PDA	6.14	5.12	1.02	0.0085

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-1.51	0.74	0.77	0.0045
5 min PDA	4.26	6.57	2.31	0.0053
15 min PDA	4.97	5.72	0.75	0.3725
25 min PDA	4.86	5.77	0.91	0.1962
35 min PDA	4.69	6.28	1.59	0.0177
35 min PDA compared to 45 min PDA	1.45	3.94	2.49	0.0011
45min PDA	6.14	9.22	3.08	0.0001

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-1.03	0.74	0.29	0.0296
5 min PDA	5.21	6.57	1.36	0.0432
15 min PDA	5.43	5.72	0.29	0.444
25 min PDA	5.39	5.77	0.38	0.2661
35 min PDA	5.07	6.28	1.21	0.023
35 min PDA compared to 45 min PDA	0.05	3.94	3.89	0.0001
45min PDA	5.12	9.22	4.1	0.0001

Heart rate (beats / minute)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-19.05	-4.2	14.85	0.0075
5 min PDA	58.19	75.8	17.61	0.0015
15 min PDA	69.01	79.18	10.17	0.1913
25 min PDA	64.48	78.01	13.53	0.1306
35 min PDA	63.8	78.1	14.3	0.0316
35 min PDA compared to 45 min PDA	34.49	-5.25	29.24	0.0041
45min PDA	98.29	72.85	25.44	0.0054

b) Etorphine compared to etorphine / azaperone

MBVR	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-19.05	-2.49	16.56	0.0036
5 min PDA	58.19	78.84	20.65	0.0064
15 min PDA	69.01	80.6	11.59	0.232
25 min PDA	64.48	85.91	21.43	0.0247
35 min PDA	63.8	88.77	24.97	0.0005
35 min PDA compared to 45 min PDA	34.49	55.68	21.19	0.0783
45min PDA	98.29	144.45	46.16	0.0001

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-4.2	-2.49	1.71	0.7063
5 min PDA	75.8	78.84	3.04	0.5706
15 min PDA	79.18	80.6	1.42	0.9425
25 min PDA	78.01	85.91	7.9	0.3607
35 min PDA	78.1	88.77	10.67	0.0508
35 min PDA compared to 45 min PDA	-5.25	55.68	50.43	0.0001
45min PDA	72.85	144.45	71.6	0.0001

Stroke volume (ml / beat)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-0.8	-8.12	7.32	0.2954
5 min PDA	74.17	71.01	3.16	0.1929
15 min PDA	72.19	69.24	2.95	0.192
25 min PDA	75.1	68.48	6.62	0.0462
35 min PDA	73.45	64.7	8.75	0.0238
35 min PDA compared to 45 min PDA	-8.52	6.82	1.7	0.0053
45min PDA	64.93	71.52	6.59	0.8034

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.8	12.25	11.45	0.1022
5 min PDA	74.17	85.61	11.44	0.156
15 min PDA	72.19	71.72	0.47	0.7925
25 min PDA	75.1	68.01	7.09	0.1512
35 min PDA	73.45	70.84	2.61	0.5087
35 min PDA compared to 45 min PDA	-8.52	-6.42	2.1	0.6725
45min PDA	64.93	64.42	0.51	0.8225

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-8.12	12.25	4.13	0.0146
5 min PDA	71.01	85.61	14.6	0.0122
15 min PDA	69.24	71.72	2.48	0.268
25 min PDA	68.48	68.01	0.47	0.4554
35 min PDA	64.7	70.84	6.14	0.07
35 min PDA compared to 45 min PDA	6.82	-6.42	0.4	0.0132
45min PDA	71.52	64.42	7.1	0.6329

APPENDIX C

OXYGEN CONSUMPTION : TABLES OF STATISTICAL PROBABILITIES

CONTENTS

ETORPHINE 170

Oxygen consumption index 170

Arterial oxygen concentration 170

Venous oxygen concentration 170

Arterial haemoglobin concentration 171

Arterial oxygen saturation 171

ETORPHINE / XYLAZINE 172

Oxygen consumption index 172

Arterial oxygen concentration 172

Venous oxygen concentration 172

Arterial haemoglobin concentration 173

Arterial oxygen saturation 173

ETORPHINE / AZAPERONE 174

Oxygen consumption index 174

Arterial oxygen concentration 174

Venous oxygen concentration 174

Arterial haemoglobin concentration 175

Arterial oxygen saturation 175

COMPARISONS BETWEEN THE THREE TREATMENTS

Oxygen consumption index 176

Arterial oxygen concentration 177

Venous oxygen concentration 178

Arterial haemoglobin concentration 179

Arterial oxygen saturation 180

OXYGEN CONSUMPTION

ETORPHINE

Oxygen consumption index (ml / min / kg)

MBVR = 4.65	Difference	Probability
MBVR compared to 15 min PDA (3.82)	-0.83	0.018
15 min PDA compared to 35 min PDA (4.19)	0.37	0.2126
MBVR compared to 35 min PDA (4.19)	-0.46	0.0815
35 min PDA compared to 45 min PDA (4.64)	0.45	0.6113
MBVR compared to 45 min PDA (4.64)	-0.01	0.7671
MBVR compared to 95 min PDA (4.02)	-0.63	0.2059

Arterial oxygen concentration (ml / 100 ml)

MBVR = 13.25	Difference	Probability
MBVR compared to 5 min PDA (14.40)	1.15	0.2234
MBVR compared to 35 min PDA (13.10)	0.15	0.7386
35 min PDA compared to 45 min PDA (14.68)	1.58	0.0268
MBVR compared to 45 min PDA (14.68)	1.43	0.0026
MBVR compared to 65 min PDA (12.93)	0.32	0.5637
MBVR compared to 95 min PDA (13.32)	0.07	0.7835

Venous oxygen concentration (ml / 100ml)

MBVR = 8.74	Difference	Probability
MBVR compared to 5 min PDA (8.38)	-0.36	0.6132
MBVR compared to 35 min PDA (8.12)	-0.62	0.7541
35 min PDA compared to 45 min PDA (10.43)	2.31	0.0008
MBVR compared to 45 min PDA (10.43)	1.69	0.0006
MBVR compared to 65 min PDA (9.18)	0.44	0.1717
MBVR compared to 95 min PDA (9.14)	0.4	0.1033

Arterial haemoglobin concentration (g / dl)

MBVR = 10.24	**Difference**	**Probability**
MBVR compared to 5 min PDA (12.1)	1.86	0.0018
MBVR compared to 35 min PDA (10.43)	0.19	0.815
35 min PDA compared to 45 min PDA (11.38)	0.95	0.0164
MBVR compared to 45 min PDA (11.38)	1.14	0.0109
MBVR compared to 65 min PDA (10.15)	0.09	0.5687
MBVR compared to 95 min PDA (10.32)	0.08	0.8002

Arterial oxygen saturation (%)

MBVR = 92.95	**Difference**	**Probability**
MBVR compared to 5 min PDA (86.44)	-6.51	0.2346
MBVR compared to 35 min PDA (90.57)	-2.38	0.4582
35 min PDA compared to 45 min PDA (92.88)	2.31	0.5295
MBVR compared to 45 min PDA (92.88)	-0.07	0.9012
MBVR compared to 95 min PDA (93.07)	0.12	0.8653

ETORPHINE / XYLAZINE

Oxygen consumption index (ml / min / kg)

MBVR = 4.93	Difference	Probability
MBVR compared to 5 min PDA (3.28)	-1.65	0.0001
5 min p.d.a compared to 35 min PDA (2.71)	-0.57	0.1174
35 min PDA compared to 45 min PDA (3.35)	-0.64	0.6113
MBVR compared to 65 min PDA (2.19)	-2.74	0.0024
65 min PDA compared to 75 min PDA (4.75)	2.56	0.0011
MBVR compared to 75 min PDA (4.75)	-0.18	0.8403
MBVR compared to 95 min PDA (3.61)	-1.32	0.0272

Arterial oxygen concentration (ml / 100ml)

MBVR = 13.15	Difference	Probability
MBVR compared to 5 min PDA (8.62)	-4.53	0.0001
MBVR compared to 35 min PDA (9.20)	-3.95	0.0001
35 min PDA (9.20) compared to 45 min PDA (10.92)	1.72	0.0166
MBVR compared to 45 min PDA (10.92)	2.23	0.0001
65 min PDA (9.50) compared to 75 min PDA (15.15)	5.65	0.0001
MBVR compared to 75 min PDA (15.15)	2	0.0004
MBVR compared to 95 min PDA (13.32)	0.17	0.706

Venous oxygen concentration (ml / 100ml)

MBVR = 8.89	Difference	Probability
MBVR compared to 5 min PDA (4.75)	-4.14	0.0001
MBVR compared to 35 min PDA (6.07)	-2.82	0.0001
35 min PDA compared to 45 min PDA (5.85)	-0.22	0.0766
MBVR compared to 65 min PDA (7.23)	-1.66	0.0371
65 min PDA compared to 75 min PDA (10.75)	3.52	0.0001
MBVR compared to 75 min PDA (10.75)	1.86	0.009
MBVR compared to 95 min PDA (9.42)	0.53	0.1344

Arterial haemoglobin concentration (g / dl)

MBVR = 10.19	**Difference**	**Probability**
MBVR compared to 5 min PDA (10.38)	0.19	0.9954
5 min PDA compared to 15 min PDA (9.37)	-1.01	0.0012
MBVR compared to 15 min PDA (9.37)	-0.82	0.0314
MBVR compared to 35 min PDA (9.12)	-1.07	0.042
35 min PDA compared to 45 min PDA (9.54)	0.42	0.2601
MBVR compared to 65 min PDA (8.93)	-1.26	0.0001
65 min PDA compared to 75 min PDA (11.85)	2.92	0.0001
MBVR compared to 95 min PDA (10.50)	0.31	0.3858

Arterial oxygen saturation (%)

MBVR = 92.84	**Difference**	**Probability**
MBVR compared to 5 min PDA (59.52)	-33.32	0.0001
MBVR compared to 35 min PDA(72.42)	-20.42	0.0001
35 min PDA compared to 45 min PDA (82.42)	10	0.002
MBVR compared to 45 min PDA (82.42)	-10.42	0.0139
65 min PDA (85.40) compared to 75 min PDA (92.02)	6.62	0.0063
MBVR compared to 75 min PDA (92.02)	-0.82	0.1529
MBVR compared to 95 min PDA (91.23)	-1.61	0.0055

ETORPHINE / AZAPERONE

Oxygen consumption index (ml / min / kg)

MBVR = 5.10	Difference	Probability
MBVR compared to 5 min PDA (3.98)	-1.12	0.0051
5 min PDA compared to 35 min PDA (2.91)	-1.07	0.0366
35 min PDA compared to 45 min PDA (7.45)	4.54	0.0001
MBVR compared to 45 min PDA (7.45)	2.35	0.0094
MBVR compared to 75 min PDA (4.48)	-0.62	0.5651

Arterial oxygen concentration (ml / 100ml)

MBVR = 13.54	Difference	Probability
MBVR compared to 5 min PDA (11.60)	-1.94	0.0256
35 min PDA (11.43) compared to 45 min PDA (14.88)	3.45	0.0001
MBVR compared to 45 min PDA (14.88)	1.34	0.0028
MBVR compared to 75 min PDA (13.70)	0.16	0.4038

Venous oxygen concentration (ml / 100ml)

MBVR = 8.84	Difference	Probability
MBVR compared to 5 min PDA (9.72)	0.88	0.6745
MBVR compared to 35 min PDA (8.92)	0.08	0.678
35 min PDA compared to 45 min PDA (10.50)	1.58	0.0289
MBVR compared to 45 min PDA (10.50)	1.66	0.0083
MBVR compared to 75 min PDA (10.43)	1.59	0.0212

Arterial haemoglobin concentration (g / dl)

MBVR = 10.53	**Difference**	**Probability**
MBVR compared to 5 min PDA (11.12)	0.59	0.1344
MBVR compared to 35 min PDA (9.30)	-1.23	0.0915
35 min PDA compared to 45 min PDA (11.65)	2.35	0.0001
MBVR compared to 45 min PDA (11.65)	1.12	0.0062
MBVR compared to 75 min PDA (10.62)	0.09	0.4093

Arterial oxygen saturation (%)

MBVR = 92.56	**Difference**	**Probability**
MBVR compared to 5 min PDA (75.67)	-16.89	0.0023
MBVR compared to 35 min PDA (88.30)	-4.26	0.1958
35 min PDA compared to 45 min PDA (92.00)	3.7	0.2038
MBVR compared to 45 min PDA (92.00)	-0.56	0.9719
MBVR compared to 75 min PDA (92.53)	-0.03	0.9712

COMPARISONS BETWEEN THE THREE TREATMENTS

Oxygen consumption index (ml / min / kg)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-0.1	-1.65	1.55	0.008
5 min PDA	4.55	3.28	1.27	0.0106
15 min PDA	3.82	3.12	0.7	0.175
25 min PDA	3.94	3.22	0.72	0.173
35 min PDA	4.19	2.71	1.48	0.0073
35 min PDA compared to 45 min PDA	0.45	0.64	0.19	0.8243
45min PDA	4.64	3.35	1.29	0.3362

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.1	-1.12	1.02	0.0938
5 min PDA	4.55	3.98	0.57	0.1016
15 min PDA	3.82	3.42	0.4	0.3612
25 min PDA	3.94	3.07	0.87	0.0721
35 min PDA	4.19	2.91	1.28	0.0171
35 min PDA compared to 45 min PDA	0.45	4.54	4.09	0.002
45min PDA	4.64	7.45	2.81	0.0412

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-1.65	-1.12	0.53	0.294
5 min PDA	3.28	3.98	0.7	0.3697
15 min PDA	3.12	3.42	0.3	0.6442
25 min PDA	3.22	3.07	0.15	0.641
35 min PDA	2.71	2.91	0.2	0.7057
35 min PDA compared to 45 min PDA	0.64	4.54	3.9	0.0024
45min PDA	3.35	7.45	4.1	0.0051

Arterial oxygen concentration (ml / 100ml)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	1.15	-4.53	3.38	0.0001
5 min PDA	14.4	8.62	5.78	0.0041
15 min PDA	13.18	8.95	4.23	0.0001
25 min PDA	12.77	9.54	3.23	0.0019
35 min PDA	13.1	9.2	3.9	0.0006
35 min PDA compared to 45 min PDA	1.58	1.72	0.14	0.8597
45min PDA	14.68	10.92	3.76	0.0001

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	1.15	-1.94	0.79	0.0201
5 min PDA	14.4	11.6	2.8	0.033
15 min PDA	13.18	11.9	1.28	0.071
25 min PDA	12.77	11.72	1.05	0.1712
35 min PDA	13.1	11.43	1.67	0.0577
35 min PDA compared to 45 min PDA	1.58	3.45	1.87	0.0706
45min PDA	14.68	14.88	0.2	0.9296

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-4.53	-1.94	2.59	0.0104
5 min PDA	8.62	11.6	2.98	0.0827
15 min PDA	8.95	11.9	2.95	0.0036
25 min PDA	9.54	11.72	2.18	0.0272
35 min PDA	9.2	11.43	2.23	0.037
35 min PDA compared to 45 min PDA	1.72	3.45	1.73	0.0987
45min PDA	10.92	14.88	3.96	0.0001

Venous oxygen concentration (ml / 100ml)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-0.36	-4.14	3.78	0.0008
5 min PDA	8.39	4.75	3.64	0.0012
15 min PDA	8.83	5.45	3.38	0.0046
25 min PDA	8.23	5.33	2.9	0.004
35 min PDA	8.12	6.07	2.05	0.0048
35 min PDA compared to 45 min PDA	2.31	-0.22	2.09	0.1139
45min PDA	10.43	5.85	4.58	0.003

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-0.36	0.88	0.52	0.5174
5 min PDA	8.39	9.72	1.33	0.7015
15 min PDA	8.83	8.7	0.13	0.7386
25 min PDA	8.23	8.85	0.62	0.7765
35 min PDA	8.12	8.92	0.8	0.6711
35 min PDA compared to 45 min PDA	2.31	1.58	0.73	0.2026
45min PDA	10.43	10.5	0.07	0.3318

c) Etorphine / xylazine compared to etorphine azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-4.14	0.88	3.26	0.0002
5 min PDA	4.75	9.72	4.97	0.0004
15 min PDA	5.45	8.7	3.25	0.0066
25 min PDA	5.33	8.85	3.52	0.0015
35 min PDA	6.07	8.92	2.85	0.0013
35 min PDA compared to 45 min PDA	-0.22	1.58	1.36	0.7183
45 min p.d.a	5.85	10.5	4.65	0.0016

Arterial haemaglobin concentration (g / dl)

a) Etorphine compared to Etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	1.86	0.19	1.67	0.0136
5 min PDA	12.1	10.38	1.72	0.0982
15 min PDA	10.73	9.37	1.36	0.0443
25 min PDA	10.28	9.35	0.93	0.5219
35 min PDA	10.43	9.12	1.31	0.1415
35 min PDA compared to 45 min PDA	0.95	0.42	0.53	0.3377
45min PDA	11.38	9.54	1.84	0.011

b) Etorphine compared to etorphine azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	1.86	0.59	1.27	0.0928
5 min PDA	12.1	11.12	0.98	0.1328
15 min PDA	10.73	10.02	0.71	0.13
25 min PDA	10.28	9.75	0.53	0.423
35 min PDA	10.43	9.3	1.13	0.148
35 min PDA compared to 45 min PDA	0.95	2.35	1.4	0.0202
45min PDA	11.38	11.65	0.27	0.9946

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	0.19	0.59	0.4	0.2835
5 min PDA	10.38	11.12	0.74	0.5788
15 min PDA	9.37	10.02	0.65	0.6415
25 min PDA	9.35	9.75	0.4	0.8991
35 min PDA	9.12	9.3	0.18	0.9712
35 min PDA compared to 45 min PDA	0.42	2.35	1.93	0.0045
45min PDA	9.54	11.65	2.11	0.0143

Arterial oxygen saturation (%)

a) Etorphine compared to etorphine / xylazine

	e	ex	Difference	Probability
MBVR compared to 5 min PDA	-6.51	-33.32	26.81	0.0016
5 min PDA	86.44	59.52	26.92	0.0025
15 min PDA	88.88	68.77	20.11	0.0003
25 min PDA	89.33	71.9	17.43	0.0003
35 min PDA	90.57	72.42	18.15	0.0019
35 min PDA compared to 45 min PDA	2.31	10	7.69	0.0435
45min PDA	92.88	82.42	10.46	0.0645

b) Etorphine compared to etorphine / azaperone

	e	ea	Difference	Probability
MBVR compared to 5 min PDA	-6.51	-16.89	10.38	0.1292
5 min PDA	86.44	75.67	10.77	0.0779
15 min PDA	88.88	85.54	3.34	0.2272
25 min PDA	89.33	86.47	2.86	0.479
35 min PDA	90.57	88.3	2.27	0.6957
35 min PDA compared to 45 min PDA	2.31	3.7	1.39	0.6338
45min PDA	92.88	92	0.88	0.6796

c) Etorphine / xylazine compared to etorphine / azaperone

	ex	ea	Difference	Probability
MBVR compared to 5 min PDA	-33.32	-16.89	16.43	0.0289
5 min PDA	59.52	75.67	16.15	0.0854
15 min PDA	68.77	85.54	16.77	0.0058
25 min PDA	71.9	86.47	14.57	0.0013
35 min PDA	72.42	88.3	15.88	0.006
35 min PDA compared to 45 min PDA	10	3.7	6.3	0.1065
45min PDA	82.42	92	9.58	0.037