Sedation and Dissociative Anaesthesia in the Horse

Physiological and Clinical aspects

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Abstract

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The overall aim of this investigation was to study the effects of different drug combinations for premedication and dissociative anaesthesia, to examine their suitability for field conditions and their ability to maintain cardiorespiratory function and provide sufficient analgesia for common, but challenging procedures such as castration.

Haemodynamic parameters, pulmonary ventilation-perfusion relationships, and clinical effects were studied during sedation and dissociative anaesthesia. The effects of additional premedication and prolongation of dissociative anaesthesia and response to surgery were evaluated.

The cardiorespiratory effects of romifidine and tiletamine-zolazepam anaesthesia did not differ significantly from those of prolonged romifidine and ketamine anaesthesia. Prolongation of anaesthesia with ketamine alone after romifidine/ketamine resulted in a poor quality of anaesthesia.

There was a decrease in arterial oxygenation during sedation with α_2-agonists, which was mainly attributed to a reduced cardiac output and increased ventilation-perfusion mismatch. During dissociative anaesthesia the cardiac output did normalise, but arterial oxygenation was further impaired as a result of increased intrapulmonary shunt and increased ventilation-perfusion mismatch. Administration of acepromazine before sedation with romifidine and butorphanol resulted in better maintenance of circulation and partly prevented the anaesthesia-induced ventilation-perfusion disturbances and fall in arterial oxygen tension. Although the arterial oxygenation was further impaired during anaesthesia and recumbency compared to that during sedation, the oxygen delivery did not decrease further. On the contrary, the arterial-mixed venous oxygen content difference and mixed venous oxygen tension remained closer to standing unsedated values during anaesthesia than in the sedated horse.

Breathing high oxygen concentrations (>95% oxygen) during dissociative anaesthesia improved arterial oxygenation compared to air breathing (21% oxygen), but concomitantly increased intrapulmonary shunt and introduced hypoventilation. The intrapulmonary shunt created during anaesthesia with high oxygen concentrations persisted when the horses returned to air breathing, possibly indicating that resorption atelectasis produced during high oxygen breathing subsequently persisted during anaesthesia and recumbency.

Tiletamine-zolazepam anaesthesia, after premedication with acepromazine, romifidine and butorphanol, produced anaesthesia and analgesia sufficient for castration of colts under field conditions. When the same regimen was used in the animal hospital there was a need for supplementary anaesthesia in some cases to complete surgery. The induction, anaesthesia and recovery were calm and without excitation in all colts both under hospital and field conditions. Cardiorespiratory changes during air breathing were within acceptable limits in these clinically healthy horses.

Key words: *horses, field anaesthesia, additional premedication, prolonging dissociative anaesthesia, respiration, circulation, pulmonary gas exchange, intrapulmonary shunt, α_2-agonists, butorphanol, acepromazine, ketamine, diazepam, tiletamine, zolazepam.*

Appendix

Papers I-VI

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I Marntell, S. & Nyman, G. 1996. Effects of additional premedication on romifidine and ketamine anaesthesia in horses. *Acta Veterinaria Scandinavica*, 37, 315-325.

II Marntell, S. & Nyman, G. 1996. Prolonging dissociative anaesthesia in horses with a repeated bolus injection. *Journal of Veterinary Anaesthesia*, 23, 64-69.

III Nyman G., Marntell S., Edner, A., Funkquist, P., Morgan, K. & Hedenstierna, G. 2004. Effect of sedation with detomidine and butorphanol on pulmonary gas exchange in the horse. (Submitted)

IV Marntell, S., Nyman, G., Funkquist, P. & Hedenstierna, G. 2003. Effects of acepromazine on pulmonary gas exchange and circulation during sedation and dissociative anaesthesia in the horse. *Veterinary Anaesthesia and Analgesia*. (Accepted)

V Marntell, S., Nyman, G. & Hedenstierna, G. 2003. High fraction of inhaled oxygen increases intrapulmonary shunt in the anaesthetised horse. *Veterinary Anaesthesia and Analgesia*. (Accepted)

VI Marntell, S., Nyman, G. & Funkquist, P. 2004. Clinical evaluation of dissociative anaesthesia during castration in colts. (Submitted)

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Abbreviations

ASAT	Aspartate aminotransferase
CaO_2	Arterial oxygen content
$C(a\text{-}v)O_2$	Arterial-mixed venous oxygen content difference
$C(a\text{-}jv)O_2$	Arterial-jugular venous oxygen content difference
CK	Creatine kinase
F_IO_2	Inspired fraction of oxygen
Hb	Haemoglobin concentrations
HR	Heart rate
HPV	Hypoxic pulmonary vasoconstriction
kPa	kilopascal
log SDQ	Logarithmic standard deviation of the perfusion distribution
log SDV	Logarithmic standard deviation of the alveolar ventilation
PAO_2	Alveolar oxygen tension
$P(A\text{-}a)O_2$	Alveolar-arterial oxygen tension difference
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PAP	Pulmonary arterial pressure
$PjvO_2$	Jugular venous oxygen tension
PvO_2	Mixed venous oxygen tension
Qmean	Mean distribution of perfusion
Qt	Cardiac output
RR	Respiratory rate
SAP	Systemic arterial pressure
SV	Stroke volume
TSR	Total systemic vascular resistance
VD/VT	Dead space to tidal volume ratio
VE	Expired minute ventilation
Vmean	Mean distribution of ventilation
VT	Tidal volume
V_A/Q	Ventilation-perfusion ratio
Qs/Qt	Intrapulmonary shunt

Abbreviations for sedative and anaesthetic protocols:

De: Detomidine
DeB: Detomidine + butorphanol
RK: Romifidine + ketamine
RBK: Romifidine + butorphanol + ketamine
RDK: Romifidine + diazepam+ ketamine
ARK: Acepromazine + romifidine + ketamine
RK+K: Romifidine + ketamine, repeated dose of ketamine
RK+RK: Romifidine + ketamine, repeated doses of both romifidine and ketamine
RZ (RT/Z): Romifidine + Zoletil®(tiletamine/zolazepam)
RBZ: Romifidine + butorphanol + Zoletil®(tiletamine/zolazepam)
ARBZ: Acepromazine+ romifidine+ butorphanol + Zoletil®(tiletamine/zolazepam)
ARBZ-O_2: Drug-combination same as ARBZ, but during anaesthesia the horses breathed more than 95% oxygen the first 15 minutes, thereafter air (21% oxygen).

Introduction

"*The success of a veterinarian as a surgeon depends in no small degree on his knowledge of anaesthetics and his skills in their administration*" *J.G. Wright 1941.*

For veterinarians working in general practice the need for knowledge of anaesthetics and skills in their administration is as great today as it was in 1941. This is especially true for veterinarians treating horses in remote areas, with many hours of driving to reach a large-animal clinic or hospital.

The horse is a large animal, entailing a risk for accidents to surrounding persons. The temperament of this animal often precludes the use of local analgesia without heavy sedation (Hall & Clarke 1991). Sedation with the α_2-adrenoceptor agonists (α_2-agonists) detomidine, romifidine and xylazine has been found useful in equine practice. The principal physiological effects of the different α_2-agonists are similar, in that they produce a reduction in heart rate, a decrease in cardiac output and initial hypertension followed by prolonged hypotension (England & Clarke 1996). The sedated horse must be handled with caution, as the animal may be aroused by stimulation and can respond with very well aimed kicks (Clarke & Taylor 1986; Hall, Clarke & Trim 2001). Thirty-one veterinary accidents involving horses were reported to the Swedish Work Environment Authority during 1997-2001, compared to 14 involving dogs (Bengtsson 2003). Sometimes the risk of injuries will be reduced and the ability to perform surgery improved if the horse is anaesthetised. However, anaesthetisation of the horse is still a challenge for the veterinarian, and the risk of mortal complications is higher for the horse than for dogs and cats (Jones 2001). The perioperative mortality rate among apparently healthy horses undergoing general anaesthesia is around 1% (Johnston *et al.* 2002). One-third of the deaths were caused by cardiac arrest, one-third originated from fractures and myopathies, and the remaining third resulted from a range of causes.

In early years inhalation anaesthesia in the horse was performed with a simple mask, where a sponge containing chloroform was applied in direct contact with the nostrils. This method was previously used in field practice for induction of anaesthesia or for administration in the restrained horse in the recumbent position. One danger associated with chloroform was cardiac failure during induction and another was delayed poisoning due to a toxic effect on the liver and kidneys (Wright 1947).

Ether, which has no delayed toxic action on the liver, could not usually be delivered in concentrations sufficient to produce surgical anaesthesia when used on an open mask in the horse. To overcome this problem, Henkels (1938) developed an apparatus for administration of ether to horses. Drawbacks with ether are its high flammability and the fact that mixtures of its vapour with oxygen or air in certain proportions are explosive. The real incentive for further development of inhalation anaesthesia for horses came from the discovery of halothane in 1956 (Hall & Clarke 1991, Jones 1993). Today inhalation anaesthesia

with halothane and isoflurane is widely used in the horse. However, the use of anaesthetic gases is better regulated today in consideration of occupational health aspects (AFS 2001:7), but bringing anaesthetic machines and all necessary equipment to the field is not possible for veterinarians working in general practice.

Castrations have long been a common but challenging surgical procedure and in the textbook Veterinary Anaesthesia of 1947 Wright describes anaesthesia for castration of the horse, both in the standing position and in the cast (recumbent) position. The cast position was preferred for large mature subjects and the standing position for one- to two-year-old colts. Hudson (1919) described standing castration under local anaesthesia and Wright modified the technique and commented that in this somewhat hampered situation (applying local anaesthetics with only a twitch applied to the upper lip), the operator must be prepared for animal movements on insertion of the needle. If it becomes necessary to make a series of stabs with the needle, the animal may become vigorous and the method will fail (Wright 1947).

In field conditions intravenous anaesthesia is usually the method of choice, as it can be performed without the facilities at hand in animal hospitals, such as induction stalls, transport systems, padded recovery rooms and skilled assisting personnel. In the absence of these facilities, anaesthetic protocols intended for use in field practice need to achieve calm induction, anaesthesia and recovery without excitation and without danger for the horse or helping personnel.

During anaesthesia, the circulation and respiration should be well maintained, with adequate oxygen delivery to the tissues and with anaesthesia and analgesia sufficient for surgery. Intravenous anaesthesia has been advocated as more favourable than inhalation on the basis of cardiorespiratory data (Taylor *et al.* 1992, 1998; Luna *et al.* 1996). Further, results of Johnston *et al.* (2000, 2002) have indicated that the mortality rate is lower with total intravenous anaesthesia than with inhalation anaesthesia. The two intravenous anaesthetics ketamine and tiletamine are both congeners to phencyclidine and are referred to as dissociative anaesthetics. Ketamine's low ability to cause cardiorespiratory depression is unequalled by other general anaesthetics (Lanning & Harmel 1975). Most of the pharmacological actions of tiletamine are similar to those of ketamine, but the duration is longer (Branson 2001).

Combinations of α_2-agonists and dissociative anaesthetics are commonly used for induction and maintenance of short-term equine anaesthesia; however, impaired arterial oxygenation is often reported (Muir *et al.* 1977, 1999, 2000; Ellis *et al.* 1977; Hall & Taylor 1981; Clarke *et al.* 1986; Hubbell *et al.* 1989, 2000; Matthews *et al.* 1991ab; Wan *et al.* 1992; Taylor *et al.* 1992, 1998; Kerr *et al.* 1996). Even when horses are ventilated with a high fraction of oxygen during anaesthesia, it is sometimes difficult to keep them well oxygenated (Hubbell *et al.* 1986). Studies of equine pulmonary dysfunctions occurring with use of different anaesthetic protocols and body positions have mainly been conducted during inhalation with 100% oxygen. Studies of the ventilation-perfusion relationship have shown that a large right to left vascular shunt develops during inhalation anaesthesia in horses (Nyman & Hedenstierna 1989; Nyman *et al.* 1990). In

human studies, inhalation of 100% oxygen during anaesthesia has been found to promote atelectasis and intrapulmonary shunt, in contrast to inhalation of 30% oxygen in nitrogen (Rothen *et al.* 1995a). No equine study has addressed the effect of breathing high oxygen concentrations on the pulmonary ventilation-perfusion ratio during dissociative anaesthesia.

Premedication with acepromazine alone or in combination with α_2-agonists has been reported to reduce the risk of anaesthetic complications (Johnston *et al.* 1995, 2000). However, the effects on the pulmonary ventilation-perfusion ratio produced by α_2-agonists alone or in combination with acepromazine during sedation and during subsequent anaesthesia in the horse have not been studied.

Although intravenous anaesthesia has been advocated on cardiorespiratory grounds, the anaesthesia and analgesia have sometimes been reported to be inadequate for surgery. In a study comparing four anaesthetic protocols for surgical removal of abdominal testis, it was found that 8 out of 32 horses had to be changed from intravenous to inhalation anaesthesia because of inadequate analgesia (Muir *et al.* 2000). In field conditions, xylazine/ketamine anaesthesia resulted in a need for supplemental thiopentone in 7 of 10 ponies, and during detomidine/ketamine anaesthesia 5 of 10 ponies needed thiopentone (Clarke *et al.* 1986).

There is a need for a reliable method of anaesthesia in equine field practice. The anaesthesia produced by α_2-agonists and ketamine is of short duration and sometimes inadequate for surgery. In our experience the short duration has also made them unsuitable for castration carried out by students. The hypothesis proposed was that dissociative anaesthesia can be improved and prolonged without impairment of the quality of induction or recovery and with maintenance of acceptable cardiorespiratory function under field conditions.

Figure 1 *The head holder evaluating the pulse quality during the first minute after induction under field conditions. Note the extended head and neck of the horse to help maintain a patent airway.*

Aims of the study

The overall aim of this investigation was to study the effects of different drug combinations for premedication and dissociative anaesthesia, to examine their suitability for field conditions and their ability to maintain cardiorespiratory function and provide sufficient analgesia for common, but challenging procedures such as castration.

The specific aims were:

1. To determine whether premedication with acepromazine, butorphanol or diazepam, in addition to romifidine, before induction of anaesthesia with ketamine, could improve the quality of anaesthesia without having adverse circulatory and respiratory effects. (Study **I**)

2. To compare the cardiorespiratory and clinical effects of romifidine/tiletamine-zolazepam anaesthesia with those of prolonged romifidine/ketamine anaesthesia. (Study **II**)

3. To evaluate the ventilation-perfusion relationships, gas exchange and cardiovascular response during sedation with an α_2-agonist (detomidine or romifidine) in combination with butorphanol or acepromazine and butorphanol, and during subsequent dissociative anaesthesia. (Studies **III-IV**)

4. To study the effect of a high fraction of oxygen on pulmonary function and gas exchange during dissociative anaesthesia in horses. (Study **V**)

5. To evaluate the cardiorespiratory function with use of three dissociative anaesthetic protocols and the suitability of these protocols for castration of colts under hospital conditions; and further, to test the most suitable of these anaesthetic protocols for castration under field conditions. (Study **VI**)

Materials and methods

Animals

This investigation was carried out on 76 clinically healthy horses. In one study (**III**) the procedures involved sedation in 7 horses. In studies **I, II, IV, V** and **VI** both sedation and subsequent anaesthesia were carried out, in total 117 times. The anaesthesia was performed with ketamine on 36 occasions and with tiletamine-zolazepam on 81 occasions. Surgical castration was performed on 57 colts (study **VI**).

Studies **I** and **II** were conducted on six Standardbred trotters, three mares and three geldings, weighing 405-540 kg (mean 450 kg) and of ages 5-14 years (mean 9 years). Study **III** comprised seven Standardbred trotters, 2 mares and 5 geldings, weighing 380-520 kg (mean 457 kg) and of ages 3-7 years (mean 5 years). Studies **IV** and **V** were performed on six Standardbred trotters, four geldings and two mares, aged between 3 and 12 years (mean 6 years) and weighing 423-520 kg (mean 470 kg). In study **VI**, a clinical investigation, there were 57 horses. This study was divided into two parts, one performed under hospital conditions and one under field conditions. Under hospital conditions 26 colts were castrated in the animal hospital at the Swedish University of Agricultural Sciences. These colts had a mean weight of 417 kg (165-623 kg) and a mean age of 2.5 years (1.5-5 years). Seven different breeds were represented: 13 Swedish warmbloods, 6 Standardbred trotters, 5 ponies (Dartmoor, Shetland, Welsh), one Coldblood trotter and one Lippizaner. Under field conditions, 31 colts with an estimated mean weight of 450 kg (390-600 kg) and a mean age of 1.5 years (1.5-2.5 years) were included. Breeds represented were 28 Swedish Warmbloods, one Arab crossbreed, one New Forest pony and one Coldblood draft horse.

Study design

Studies **I, II, IV** and **V** were randomised crossover studies and Studies **III** and **VI** were treatment response studies. In study **VI** the part carried out under hospital conditions was randomised. In studies **I, II, IV, V** and **VI**, measurements and sampling were performed in the standing unsedated horse (Baseline), in the sedated horse (Sedation), during anaesthesia, and after anaesthesia (Post). Sedation measurements were made in the standing horse 2-8 minutes after the sedative drugs were administered. Measurements during anaesthesia were made 5, 15, 25 and 35 minutes after the horse had entered lateral recumbency. Post measurements were performed approximately 5 minutes after the horse had retuned to a standing position. In study **III**, measurements and sampling were performed 15 minutes after sedation with detomidine and 15 minutes after subsequent butorphanol administration.

Study procedure

In all horses food was withheld for 10-12 hours prior to anaesthesia, but access was given to straw bedding and water. In 25 of the horses castrated under field

conditions, access was allowed to grass pasture. Before induction of anaesthesia, pads of cotton wool were placed in the horse´s ears to reduce external stimuli. During induction one person held the halter and in studies **IV-VI** one person held the tail or a tail rope for balance, to prevent the horse from falling forward. After induction, the horse was left undisturbed for one minute, but the head and neck were extended to help maintain a patent airway (Fig. 1). The eyes were protected with a piece of cloth. The horses were not intubated in studies **I**, **II** and **VI**, but in studies **IV** and **V** intubation was necessary to measure the ventilation and sample expired gases. The horses breathed spontaneously throughout all studies. The horses were placed in lateral recumbency in all studies and in dorso-lateral recumbency during surgical procedures in study **VI**, with the chest mainly in the lateral and the hindquarters in the dorsal position (Figs. 3 and 4). After completion of surgery the horse was returned to lateral recumbency. In study **VI** each hind leg was held with a rope or supported with straw bales, a safety precaution that also kept the horse in balance and gave the surgeon access to the surgical area. The ear pads were removed approximately 45 minutes after induction. The horses were never forced to stand in any study, nor were they helped to stand in studies **I** and **II** or in the part performed at the animal hospital in study **VI**. Under field conditions in study **VI** and in studies **IV** and **V,** one person held the halter and one person held the tail when the horse attempted to stand.

Catheterisation

In studies **I-V** catheterisations were performed with the horse standing and unsedated, after local analgesia with lidocaine (Xylocain® 2%, Astra, Södertälje, Sweden). A catheter was introduced percutaneously into the facial artery (18G, Hydrocath TM arterial catheter, Omeda, UK) and an infusion catheter (14G, Intranule, Vygone, France) was placed in the left jugular vein. In studies **III-V** a second infusion catheter was placed in the left jugular vein. A thermodilution catheter (7F, Swan-Ganz, Edwards lab., Santa Ana, CA, USA) was inserted with an introducer kit (8F, Arrow Int. Inc., Reading, PA, USA) through the right jugular vein into the pulmonary artery. A pigtail catheter (Cook Europe A/S, Söborg, Denmark) was introduced by the same technique into the right jugular vein, advanced to the right ventricle and then retracted into the right atrium. The venous catheters were positioned under pressure-tracing guidance. Once correctly placed, the catheters were locked in position with Luer-lock adapters. In study **VI** one infusion catheter (14G, Intranule, Vygone, France) was placed in the jugular vein before induction. Under hospital conditions a facial artery catheter was placed immediately after induction of anaesthesia.

Anaesthetic protocols

The anaesthetic protocols used within the frame of the study were randomised and at least 7 days' rest was allowed between them. All drugs were administered intravenously (i.v.) except for acepromazine (Plegicil® vet, 10 mg/ml, Pherrovet AB or Pharmacia & Upjohn Animal Health, Sweden), which was always given intramuscularly (i.m.). The horses breathed air (F_IO_2=0.21) spontaneously during anaesthesia, except in protocol ARBZ-O_2, where they spontaneously breathed a high fraction of oxygen (F_IO_2>0.95) in the first 15 minutes of anaesthesia and thereafter air. The different sedative and anaesthetic protocols were as follows:

DeB: Sedation was induced with detomidine 0.02 mg/kg (Domosedan® vet. 10 mg/ml, Orion Pharma Animal Health, Sollentuna, Sweden). After 20 minutes butorphanol 0.025 mg/kg (Torbugesic® 10 mg/ml, Fort Dodge, Iowa, USA) was administered.

RK: Sedation was induced with romifidine 0.1 mg/kg (Sedivet® vet., 10 mg/ml, Boehringer Ingelheim Vetmedica, Malmö, Sweden); 7 minutes later anaesthesia was induced with ketamine 2.2 mg/kg (Ketaminol® 100 mg/ml, Veterinaria AG, Zürich, Switzerland).

RBK: Romifidine 0.1 mg/kg; followed 2 minutes later by butorphanol 0.025 mg/kg. After a further 5 minute anaesthesia was induced with ketamine 2.2 mg/kg.

RDK: Romifidine 0.1 mg/kg; 7 minutes later anaesthesia was induced with ketamine 2.2 mg/kg. Diazepam 0.05 mg/kg (Apozepam® 5mg/ml Apothekernes laboratorium, Oslo, Norway) was administered immediately before the ketamine.

ARK: Acepromazine 0.025 mg/kg was given 23 minutes before romifidine 0.1 mg/kg, and 7 minutes after romifidine administration anaesthesia was induced with ketamine 2.2 mg/kg.

RK+K: Romifidine 0.1 mg/kg; 7 minutes later anaesthesia was induced with ketamine 2.2 mg/kg. A repeated dose of ketamine 1.1 mg/kg was given 18-20 minutes after the start of the first ketamine injection used for induction.

RK+RK: Romifidine 0.1 mg/kg; 7 minutes later anaesthesia was induced with ketamine 2.2 mg/kg. Repeated doses of both romifidine 0.04 mg/kg and ketamine 1.1 mg/kg were given 18-20 minutes after the start of the first ketamine injection used for induction.

RZ: Romifidine 0.1 mg/kg; 7 minutes later anaesthesia was induced with 1.4 mg/kg Zoletil® (tiletamine 0.7 mg/kg in combination with zolazepam 0.7 mg/kg [Zoletil 100® 100 mg/ml, Virbac, Carros, France]).

RBZ: Romifidine 0.1 mg/kg; followed one minute later by butorphanol 0.025 mg/kg. Twelve minutes after romifidine, anaesthesia was induced with 1.4 mg/kg Zoletil®.

ARBZ and ARBZ-O_2: Acepromazine 0.035 mg/kg was given 20 minutes before romifidine 0.1 mg/kg, followed one minute later by butorphanol 0.025 mg/kg. Twelve minutes after romifidine, anaesthesia was induced with 1.4 mg/kg Zoletil®.

Clinical investigation:

The RZ-hospital group: Romifidine 0.11 mg/kg (range 0.1-0.14 mg/kg); Seven minutes after romifidine, anaesthesia was induced with 1.4 mg/kg Zoletil®

The ARZ-hospital group: Acepromazine 0.033 mg/kg (range 0.025-0.05 mg/kg); 30-45 minutes later romifidine 0.11 mg/kg (range 0.1-0.15 mg/kg). Seven minutes after romifidine administration, anaesthesia was induced with 1.4 mg/kg Zoletil®.

The ARBZ-hospital group: Acepromazine 0.045 mg/kg (range 0.045-0.05 mg/kg); 30-45 minutes before romifidine 0.1 mg/kg, followed one minute later by butorphanol 0.025 mg/kg. Seven minutes after romifidine administration, anaesthesia was induced with 1.4 mg/kg Zoletil®.

The ARBZ-field group: Acepromazine 0.035 mg/kg 20-45 minutes before romifidine 0.1 mg/kg, followed one minute later by butorphanol 0.025 mg/kg. Five to 7 minutes after romifidine administration, anaesthesia was induced with 1.4 mg/kg Zoletil®.

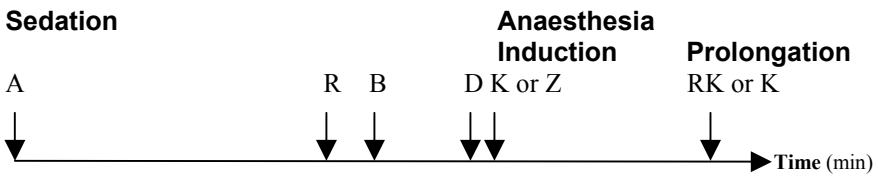

Figure 2 *Schematic drawing of time between drug administrations in the different anaesthetic protocols.*

Table 1 *Summary of sedative and anaesthetic protocols used and number (n) of horses investigated with the respective protocol.*

Protocol		Sedation		Anaesthesia		Study
DeB	(n=7)		De B	No anaesthetics given		**III**
RK	(n=6)		R	K		**I**
RBK	(n=6)		R B	K		**I**
ARK	(n=6)	A	R	K		**I**
RDK	(n=6)		R	K		**I**
RK + RK	(n=6)		R	K	RK	**II**
RK + K	(n=6)		R	K	K	**II**
RZ	(n=12)		R	Z		**II, VI**
ARZ	(n=11)	A	R	Z		**VI**
RBZ	(n=6)		R B	Z		**IV**
ARBZ	(n=46)	A	R B	Z		**VI, V, IV**
ARBZ-O_2	(n=6)	A	R B	Z		**V**

De=detomidine, B=butorphanol, A=acepromazine, R=romifidine, D=diazepam, K=ketamine and Z=Zoletil® (tiletamine and zolazepam).

Time measurements and quality assessments

The time from injection of ketamine or Zoletil® to lateral recumbency was recorded in studies **I**, **II** and **IV-VI,** and the time to muscle relaxation in studies **I** and **II**. The duration of surgery was recorded in study **VI** and the lengths of time in lateral and sternal recumbency were recorded in studies **I**, **II** and **IV-VI**. The quality of induction, anaesthesia and recovery was assessed subjectively in studies **I** and **VI**, using a 0 to 3 scale, where 0=poor, 1=fair, 2=good and 3=very good.

Response to noxious stimuli and surgery

In studies **I** and **II** the response to noxious stimuli was tested by the pin-prick method on the coronary band of the front and hind leg, the shoulder and the gaskin. If purposeful skeletal muscle movement was observed at any of the 4 test sites, this was interpreted as a response. In study **VI** the surgeon, blinded with respect to the anaesthetic protocol, decided whether supplementary anaesthesia was needed to complete the surgical procedure performed under hospital conditions.

Measurements of haemodynamic parameters

Cardiac output (Qt) was determined by the thermodilution technique (Muir *et al.* 1976; Nyman & Hedenstierna 1988). A bolus of 20 ml ice-cold 0.9% saline was rapidly injected into the right atrium through the pigtail catheter and the temperature was measured through a Swan-Ganz catheter. Cardiac output was then calculated by a cardiac output computer (Cardiac Output Computer Model 9520 A, Edwards Lab., Santa Ana, CA, USA). Systemic arterial and pulmonary arterial blood pressure (SAP and PAP) were measured by connecting the arterial catheters via fluid-filled lines to calibrated pressure transducers (Baxter Medical AB, Eskilstuna, Sweden) positioned at the level of the scapulo-humeral joint when the horse was standing and at the level of the sternal manubrium in lateral recumbency. Blood pressure and electrocardiogram (ECG) were recorded on an ink-jet recorder (Sirecust 730, Siemens-Elema, Solna, Sweden). Heart rate (HR) was measured by auscultation or palpation or was recorded from the ECG.

Measurements of pulmonary function and gas exchange

Respiratory rate (RR) was measured by observing the costo-abdominal movements in all studies. Expired minute ventilation (VE) was measured with a Tissot spirometer (Collins Inc., Braintree, MA, USA) in the standing horse in studies **III**, **IV** and **V**. Respiratory rate and tidal volume (VT) were measured at the mouthpiece of the endotracheal tube during anaesthesia in studies **IV** and **V**, using side stream spirometry (Capnomac Ultima, Datex, Finland) (Moens *et al.* 2003).

Arterial (a), mixed venous (v) or jugular venous (jv) blood samples for measurements of oxygen and carbon dioxide tensions (PaO_2, PvO_2, $PjvO_2$, $PaCO_2$, $PvCO_2$) and oxygen saturation of haemoglobin (SaO_2, SvO_2) were drawn simultaneously and anaerobically into heparinised syringes and stored on ice until analysed by means of conventional electrode techniques (ABL 5 or ABL 300,

Radiometer, Copenhagen, Denmark). Haemoglobin concentration (Hb) was determined spectrophotometrically (Ultrolab system, 2074 Calculating Absorptiometer LKB Clinicon, Bromma, Sweden or Celtin 3500, Abbott Scandinavia AB, Solna, Sweden). Blood samples for Hb measurements were taken at baseline and during sedation in studies **III**, **IV** and **V**, and during anaesthesia in studies **IV**, **V** and **VI**.

Samples of blood and expired gas for measurements of gas concentration by the multiple inert gas elimination technique were taken at baseline and during sedation in studies **III, IV** and **V** and also at 15 and 25 minutes of anaesthesia in studies **IV** and **V**. The distribution of ventilation and perfusion (V_A/Q) was estimated by the multiple inert gas elimination technique (Wagner *et al.* 1974a; Hedenstierna *et al.* 1987). Six gases (sulphur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether and acetone), inert in the sense of being chemically inactive in blood, were dissolved in isotonic Ringer acetate solution (Pharmacia, Stockholm, Sweden) and infused into the jugular vein at 30 ml/min. Arterial and mixed venous blood samples were drawn and simultaneously mixed expired gas was collected from a heated mixing box connected to a nose mask (standing measurements) or connected to the tracheal tube (anaesthesia measurements). Gas concentrations in the blood samples and expirate were measured by the method of Wagner *et al.* (1974a), using a gas chromatograph (Hewlett Packard 5890 series II, Atlanta, GA, USA). The arterial/mixed venous and mixed expired/mixed venous concentration ratios of each gas (retention and excretion, respectively) depend on its blood-gas partition coefficient and the V_A/Q of the lung. The retention and excretion were calculated for each gas, and the solubility of each gas in blood was measured in each horse by a two-step procedure (Wagner *et al.* 1974b). The solubilities were similar to those reported from a previous study (Hedenstierna *et al.* 1987). These data were then used for deriving the distribution of ventilation and blood flow in a 50-compartment lung model, with each compartment having a specific V_A/Q ratio ranging from zero to infinity. Ventilation and blood flow in healthy subjects have a log normal distribution against V_A/Q ratios. This means that the distributions of ventilation and of blood flow against V_A/Q ratios intersect each other at a V_A/Q of 1, that perfusion exceeds ventilation in regions with V_A/Q ratios below 1, and that ventilation exceeds perfusion in compartments with V_A/Q ratios above 1. Of the information obtained concerning the V_A/Q distribution, data are presented for the mean and standard deviation of the blood flow log distribution (Qmean and log SDQ, respectively), shunt (perfusion of lung regions with $V_A/Q < 0.005$), and the mean and standard deviation of the ventilation log distribution (Vmean and log SDV, respectively). All subdivisions of blood flow and ventilation are expressed in per cent of cardiac output and expired minute ventilation, respectively. The difference between measured PaO_2 and PaO_2 predicted on the basis of the amount of ventilation-perfusion mismatching and shunt (predicted-measured PaO_2) was determined. This difference reflects diffusion limitation.

Measurements of lactate and muscle enzymes

Venous blood samples were taken from four horses 24 hours after anaesthesia with protocols ARK, RBK, RDK, RK+K, RK+RK and RZ for measurements of aspartate aminotransferase (ASAT) and creatine kinase (CK), which were made

with a kinetic UV test (Konelab 30, Kone Instruments Espoo, Finland). Venous blood samples were collected at baseline, during sedation, at the beginning of anaesthesia, at the end of anaesthesia and after standing from two horses with protocols RZ, ARK and RK+K and one horse with protocols RBK, RDK and RK+RK, for measurements of plasma lactate concentrations with an enzymatic lactate analyser (Anolox GM-7, Anolox Instruments Ltd, London, UK).

Calculations and statistics

From the measured values obtained, the following calculations were made, using standard equations:
Stroke volume (SV) = Qt/HR
Total systemic vascular resistance (TSR) = mean SAP/Qt.
Arterial, mixed venous or jugular venous oxygen content (CyO_2) = Hb (g/100 ml) *x* 1.39 *x* SyO_2 + PyO_2 *x* 0.003 (y = a, v or jv).
Arterial-mixed venous or arterial-jugular venous oxygen content difference ($C(a\text{-}z)O_2$) = $CaO_2 - CzO_2$ (z = v or jv).
Expired minute ventilation (VE) = VT *x* RR.
Alveolar oxygen tension (PAO_2) = inspired oxygen tension (P_IO_2) – ($PaCO_2$/R), where R (a constant) = 0.8.
Alveolar-arterial oxygen tension differences ($P(A\text{-}a)O_2$) = $PAO_2 - PaO_2$.
Oxygen delivery = CaO_2 *x* Qt.
Oxygen uptake = Qt *x* $C(a\text{-}v)O_2$.

For statistical analysis the Statistica software package (Statsoft Inc., Tulsa, OK, USA) was used. The physiological data were analysed by one-way or two-way analysis of variance for repeated measures (ANOVA). When the ANOVA indicated a significant difference or interaction, Tukey's HSD post hoc test or planned comparison was applied to describe the patterns of differences. Time measurements were compared by the Wilcoxon rank-sum test. A p value of < 0.05 was considered significant in all tests. Results are given as mean values ± SE in studies **I-II** and as mean values ± SD in studies **III-VI**.

Figures 4 & 5 *Castration performed with students Under field conditions.*

Results and discussion

Additional premedication

Controlled and smooth induction of anaesthesia is important, particularly under field conditions (Matthews & Hartsfield 1993). The use of α_2-agonists and ketamine results in good induction, with retention of muscle tonus during the induction procedure. The horse first sits down on its hind legs and then turns to the side when lying down. These inductions are easily controlled with one person holding the horse's halter. A disadvantage previously noted with romifidine and ketamine anaesthesia was that in some horses rigidity and muscle twitching persisted during anaesthesia (Marntell *et al.* 1994). Inclusion of acepromazine in the premedication in study **I** resulted in inductions of good quality, with preserved muscular tone and a significantly shorter induction time, 74±6 seconds, compared to 118±10 seconds for romifidine and ketamine alone (Table 2). Addition of a benzodiazepines, diazepam in study **I** and zolazepam in study **II**, provided good muscle relaxation during induction and anaesthesia. One disadvantage observed, however, was that in some horses muscle relaxation occurred before the induction of anaesthesia, sometimes resulting in an abrupt fall towards the person holding the head. This can be prevented by the use of a tail or tail rope holder to balance the fall.

In studies **I** and **II,** the response to noxious stimuli appeared 5-10 minutes before the horse rolled from lateral to sternal recumbency. The recovery from short-term anaesthesia is a critical period; if the horse attempts to stand before it is capable of supporting itself adequately, the resulting struggle and ataxia can lead to injury of the horse and/or bystanders (Brouwer 1985). It is preferable that the horse rests undisturbed in sternal recumbency before standing. Interestingly and somewhat unexpectedly, additional premedication with butorphanol resulted in a significantly longer time spent in sternal recumbency, 19±5 minutes compared to 8±2 minutes with romifidine and ketamine alone. One mare, which always rose immediately from the lateral to the standing position without resting in the sternal position with all other protocols both in studies **I** and **II**, rested for 12 minutes in the sternal position after receiving butorphanol. The horses reached a standing position at the first attempt after all protocols in both studies **I** and **II**. When the protocol had included diazepam or zolazepam, the recovery was slightly more ataxic, especially in the individuals spending no or only a short time in sternal recumbency.

In study **I**, administration of the α_2-agonist romifidine resulted in a significantly decreased heart rate accompanied by second-degree atrioventricular (AV) block. Administration of ketamine after premedication with romifidine returned the heart rate to baseline values, but the arterial blood pressure was significantly increased. The arterial oxygen tension decreased significantly during sedation and anaesthesia. The cardiorespiratory changes are in conformity with previous reports after sedation with α_2-agonists and anaesthesia with ketamine (Muir *et al.* 1977; Hall & Taylor 1981; Clarke *et al.* 1986; England *et al.* 1992; Kerr *et al.* 1996). Additional premedication with butorphanol or diazepam did not alter the influence of romifidine or ketamine on the cardiorespiratory parameters. Inclusion of

acepromazine in the premedication maintained the haemodynamic parameters closer to the standing unsedated values.

Table 2 *The mean length of time, ± SE, from ketamine administration to lateral recumbency (induction), to muscle relaxation, to noxious stimulus response and to standing, and the time spent in lateral and sternal recumbency, with different anaesthetic protocols.*

Anaesthetic Protocol	Induction time (sec)	Time to muscle relaxation (min)	Time to noxious stimulus response (min)	Time in lateral recumbency (min)	Time in sternal recumbency (min)	Time to standing (min)
RK	118±10	3.5±0.5	18±6	27±2	8±2	37±4
ARK	74±6*	2.8±0.4	22±2	32±2	7±3	39±4
RDK	103±8	1.9±0.3*	31±2#	38±4	6±2	45±5
RBK	96±4	3.9±2.5	27±3	32±3	19±5*	51±7

RK=romifidine and ketamine, ARK=acepromazine romifidine and ketamine, RDK=romifidine, diazepam and ketamine, RBK=romifidine, butorphanol and ketamine. ***** *= Significantly different from all other combinations.* **#** *= Significantly different from RK and ARK.*

Prolongation of dissociative anaesthesia

The minor cardiorespiratory depression produced by dissociative anaesthetics makes them suitable for field anaesthesia, but a disadvantage, especially in the horse, is the variation in the individual time spent in anaesthesia and the often abrupt recovery. The altered reflex pattern after administration of dissociative anaesthetics compared to inhalation anaesthesia (Guedel 1937; Campbell & Lawson 1958) makes it difficult to evaluate the progress of anaesthetic depth. A lack of response to surgery has been suggested as the most reliable sign of adequate anaesthetic depth during dissociative anaesthesia (Hall & Clarke 1991). In field practice prolongation of anaesthesia is often required, if the horse wakens sooner than expected or the surgical procedure is lengthened by complications. If the anaesthesia has to be performed without skilled assistants, it could be an advantage if further anaesthesia could be given on a time basis.

In study **II** the effects of prolongation of dissociative anaesthesia were investigated. A repeated injection of ketamine (RK+K) or of both ketamine and romifidine (RK+RK) was given 18 minutes after the horses had assumed lateral recumbency. This time was based on results from a previous investigation, in which no horse above 350 kg showed signs of light anaesthesia before 18 minutes (Marntell *et al.* 1994). The use of ketamine alone for prolongation was chosen because the effect of romifidine has been reported to last longer than that of xylazine and detomidine (England *et al.* 1992). In the third protocol in the comparison, anaesthesia was induced with a bolus injection of tiletamine-zolazepam (RZ) instead of ketamine. Ketamine and tiletamine are both congeners to phencyclidine and are referred to as dissociative anaesthetics, and most of the pharmacological actions of tiletamine are similar to those of ketamine (Branson 2001). Tiletamine is commercially available in a combination with zolazepam (Zoletil®). The drug combination is reconstituted in sterile water; this provides both tiletamine and zolazepam, in equivalent doses. Doses of this preparation are expressed in milligrams of the drug combination, e.g. 1.4 mg/kg Zoletil (0.7

mg/kg tiletamine and 0.7 mg/kg zolazepam). Tiletamine-zolazepam and α_2-agonists have been reported to produce a longer duration of anaesthesia in horses compared to α_2-agonists and ketamine (Matthews *et al.* 1991a) and are possible alternatives during field anaesthesia for longer procedures.

The anaesthesia with tiletamine-zolazepam and the prolonged anaesthesia produced with both romifidine and ketamine were smooth. When ketamine was given alone for prolongation, at 18 minutes of anaesthesia, the horses showed more muscle twitching and leg rigidity compared to prolongation with both ketamine and romifidine. When the anaesthesia was prolonged with ketamine alone, one horse galloped in its sleep and another horse rose to the sternal position, but no contact could be established and the head was held down, and after 2 minutes the horse relaxed in lateral recumbency. The initial injection of romifidine did not give sufficient muscle relaxation to abolish the catalepsy following a repeated injection of ketamine. It is possible that an injection of ketamine earlier in the anaesthesia would have produced less catalepsy. However, on the basis of the present results repeated injection of ketamine alone cannot be recommended after sedation with romifidine. There was no difference between the three protocols (RK+K, RK+RK and RZ) in the average time to response to noxious stimuli. The average time spent in lateral recumbency was 38 minutes with protocol RK+K (Table 3), significantly shorter than with the other two protocols RZ and RK+RK in study **II**.

Table 3 *The average time spent in lateral and sternal recumbency and time from induction until standing again, with all anaesthetic protocols used in the studies.*

Protocol		Average time (range) in lateral recumbency (min)	Average time (range) in sternal recumbency (min)	Average time (range) from induction until standing again (min)
RK	(n=6)	27 (20-36)	8 (0-18)	37 (20-45)
ARK	(n=6)	32 (23-40)	7 (0-16)	39 (23-51)
RBK	(n=6)	32 (20-42)	19 (7-40)	51 (32-78)
RDK	(n=6)	38 (27-57)	6 (0-10)	45 (27-62)
RK + K	(n=6)	38 (35-46)	5 (0-13)	43 (35-51)
RK + RK	(n=6)	43 (40-49)	6 (0-16)	49 (40-55)
RZ	(n=6)	45 (36-55)	11(0-33)	56 (36-66)
RBZ	(n=6)	61 (46-74)	4 (0-10)	65 (53-82)
ARBZ	(n=6)	65 (40-86)	5 (0-13)	70 (43-86)
ARBZ-O_2	(n=6)	67 (40-81)	4 (0-12)	71 (51-82)
RZ-hospital	(n=6)	48	10	58
ARZ-hospital	(n=11)	52	12	74
ARBZ-hospital	(n=9)	61	12	73
ARBZ-field	(n=31)	49 (31-73)	6 (0-23)	55 (32-78)

Physiological effects of sedation

Ventilation and gas exchange

Decreased arterial oxygen tension was observed during sedation in studies **I-V**. Impaired arterial oxygenation has been reported during sedation of horses with romifidine alone or in combination with butorphanol (Clarke *et al.* 1991) and during sedation with detomidine alone or in combination with butorphanol (Short *et al.* 1986; Lavoie *et al.* 1996). The decrease in PaO_2 during detomidine sedation (**III**) could mainly be attributed to reduced cardiac output and increased V_A/Q mismatch, hypoventilation increased after subsequent butorphanol administration (Fig. 5).

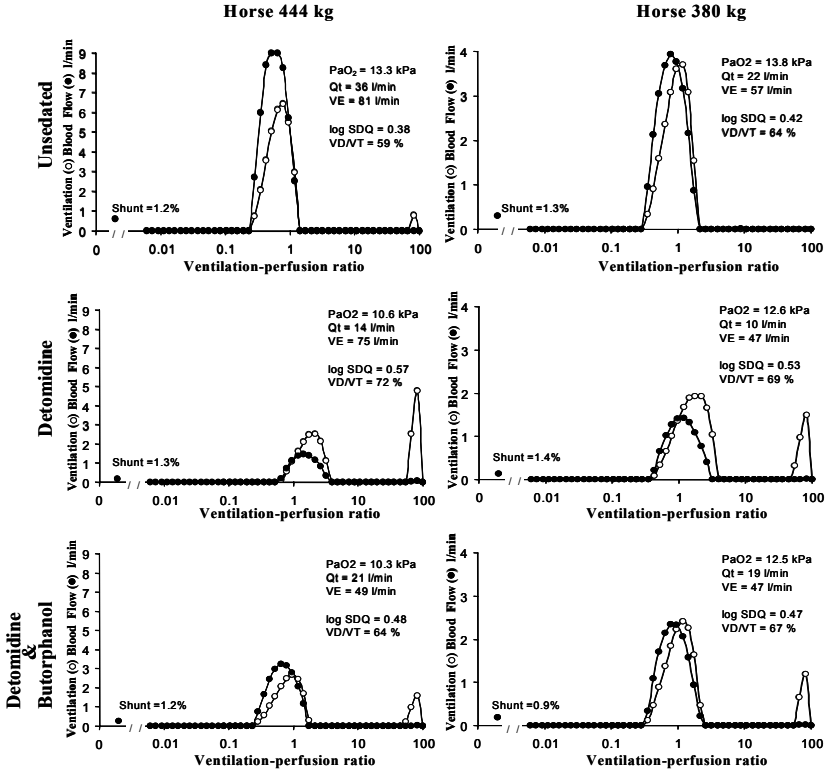

Figure 5 *Distribution of ventilation-perfusion ratio (V_A/Q) in two horses (444 kg and 380 kg). The top panels represent the V_A/Q distribution in standing horses (Unsedated). The middle panels represent the V_A/Q distribution 15 minutes after detomidine sedation (Detomidine). The lower panels represent the V_A/Q distribution 15 minutes after additional sedation with butorphanol (Detomidine & Butorphanol). Note the impaired arterial oxygen tension (PaO_2) during sedation in both the middle and bottom panels. During sedation with detomidine, cardiac output (Qt) decreased and there was an increase in ventilation-perfusion mismatch (broader base of ventilation-perfusion ratio and increased SD of blood flow log distribution (log SDQ) compared to the unsedated horses. The intrapulmonary shunt was minimal. During sedation with detomidine and butorphanol, the impaired PaO_2 was a result of increase in ventilation-perfusion mismatch and both Qt and expired minute ventilation (VE) were lower than in the unsedated horse.*

The decrease in PaO_2 during sedation with romifidine and butorphanol was also attributed to reduced cardiac output and increased V_A/Q mismatch (Fig. 6). Hypoventilation, right to left vascular shunt and diffusion limitation of oxygen were negligible, as assessed by the multiple inert gas elimination technique. Cardiac output was significantly higher during sedation including acepromazine, compared to sedation without acepromazine. The sedation protocol ARBZ, including acepromazine, maintained log SDQ at baseline value (**IV**). A reduction in cardiac output can cause a fall in PvO_2, which results in a fall in PaO_2 for the same degree of ventilation-perfusion mismatch (West 1987). Thus, the reduced cardiac output in protocol RBZ during sedation may have contributed to the reduction in PvO_2 and PaO_2, especially since a slight but significant increase in V_A/Q mismatch was observed concurrently. Further, the decrease in cardiac output may cause a larger vertical difference in perfusion in upper than in lower lung regions. This may increase V_A/Q mismatch.

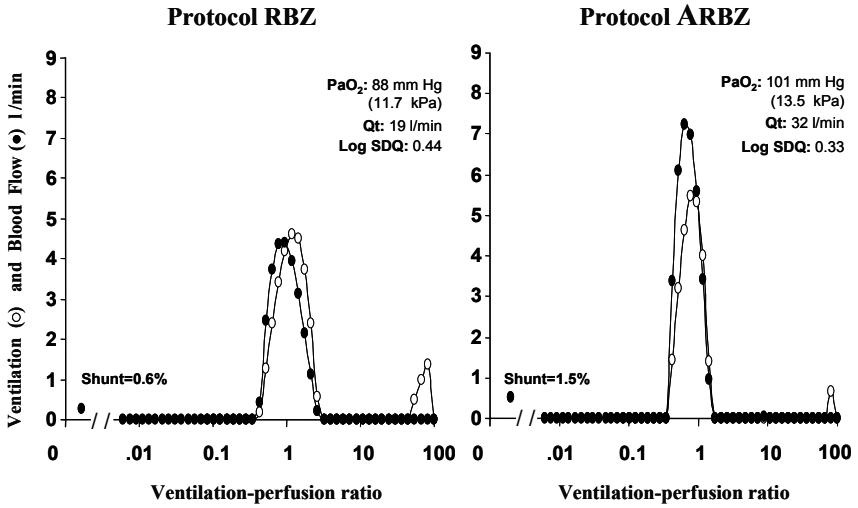

Figure 6 *Distribution of ventilation-perfusion ratio (V_A/Q) in one horse with different sedation protocols. In protocol RBZ romifidine and butorphanol were administered and in protocol ARBZ acepromazine, romifidine and butorphanol were given. During sedation the cardiac output (Qt) and arterial oxygen tension (PaO_2) were lower and ventilation-perfusion mismatch (log SDQ) was higher in protocol RBZ than in ARBZ. The intrapulmonary shunt was similar to the baseline value of the unsedated horse in both protocols. Note the good matching of ventilation and perfusion and the narrow base of the ventilation-perfusion ratio in protocol ARBZ.*

Circulation

The decrease in cardiac output during sedation with romifidine and butorphanol (**IV-V**) and detomidine (**III**) is in line with earlier reports after sedation with α_2-agonists in horses (Muir *et al.* 1979; Wagner *et al.* 1991; Yamashita *et al.* 2000; Freeman *et al.* 2002). Inclusion of acepromazine in the sedation resulted in better maintained cardiac output (**IV**). In halothane-anaesthetised horses, injection of acepromazine increased cardiac output through an increased stroke volume, while injection of the α_2-agonist xylazine resulted in decreased cardiac output due to a

decreased heart rate (Steffey *et al.* 1985). In study **IV** there was no difference in stroke volume between protocols, indicating that the higher cardiac output in the sedation including acepromazine was attributed to a better maintained heart rate. Better maintenance of the heart rate during sedation was also found in study **I,** where sedation with acepromazine and romifidine improved the heart rate compared to romifidine alone. The reason for this effect may be reversal of reflex bradycardia and/or alteration of vagal and/or sympathetic tone. Sedation including acepromazine also prevented the significant increase in TSR and mean SAP (**IV**). Sedation with acepromazine and xylazine is reported to abolish the increase in arterial pressure caused by xylazine on its own (Muir *et al.* 1979). Acepromazine used alone in horses results in hypotension (Muir *et al.* 1979; Parry *et al.* 1982) and is reported to increase digital blood flow, an effect proposed to be the result of decreased peripheral resistance, due to blockade of α-receptors (Hunt *et al.* 1994). The reason for the abolition of the increases in SAP and TSR in the present study may be that vasoconstriction produced by romifidine is counteracted by vasodilatation caused by acepromazine, or that acepromazine blocks postsynaptic α-receptors, inhibiting the vascular effects of romifidine. The exact pharmacological receptor mechanism underlying acepromazine's ability to maintain the circulatory parameters closer to baseline values during sedation with α_2-agonists remains to be clarified.

Physiological effects of anaesthesia

Ventilation and gas exchange

The impaired arterial oxygenation observed in studies **I**, **II**, **IV**, **V** and **VI** during dissociative anaesthesia is in accordance with earlier findings (Muir *et al.* 1977, 1999; Hall & Taylor, 1981; Hubbell *et al.* 1989; Matthews *et al.* 1991a; Wan *et al.* 1992). Some horses displayed an apneustic breathing pattern (Biot's breathing), where several breaths are taken quickly, followed by a pause. This has been noted in several investigations during both ketamine and tiletamine-zolazepam anaesthesia in horses (Ellis *et al.* 1977; Hubbell *et al.* 1989; Matthews *et al.* 1991a). In our investigation the altered breathing pattern in some individuals did not affect the respiratory rate, minute ventilation or increased $PaCO_2$ during anaesthesia. Additional premedication with butorphanol or diazepam did not, in study **I,** alter the influence of romifidine and ketamine on the cardiorespiratory parameters. The decreased PaO_2 during dissociative anaesthesia observed in study **IV** could mainly be attributed to a significant increase in shunt and V_A/Q mismatch. Hypoventilation and diffusion limitation of oxygen were negligible.

In study **II**, there were no significant differences in cardiorespiratory parameters between the protocols RK+K, RK+RK and RZ. With protocol RZ the lowest mean PaO_2 (8.0 kPa) was noted 5 minutes after induction of anaesthesia, while the lowest mean value with RK anaesthesia (8.7 kPa) was noted when the anaesthesia was prolonged with both the α_2-agonist and ketamine. Interestingly, the lowest PaO_2, in both protocol RZ and RK+RK, was observed at the same time as the most pronounced increase in mean arterial blood pressure. Inclusion of acepromazine in the protocol (study **IV**) resulted in a higher PaO_2 and higher arterial oxygen saturation compared to the protocol without acepromazine. The increased

ventilation/perfusion mismatch in the protocol without acepromazine contributed to greater impairment of arterial oxygenation (Fig. 7). An explanation for the increased mismatch could be the significantly elevated PAP with RBZ compared to ARBZ (Fig. 8). It has been reported that increased pulmonary vascular pressure attenuated hypoxic pulmonary vasoconstriction (HPV) in dogs (Benumof & Wahrenbrock 1975). HPV is important for the distribution of blood flow from hypoxic regions in the lung to ventilated areas. Since it is suggested that the pony has a stronger HPV response than the dog (Elliott *et al.* 1991), it is possible that a pre-existing increased PAP in the horse may disturb HPV, contributing to a further decrease in arterial oxygenation in the protocol without acepromazine.

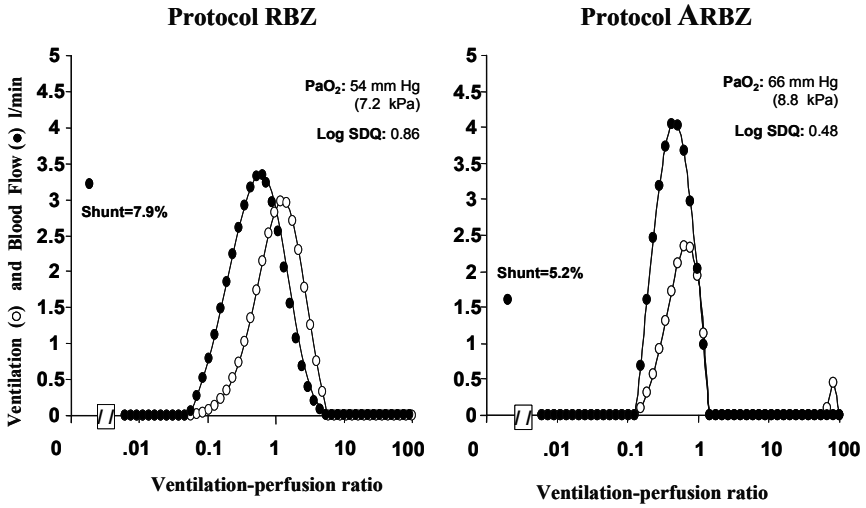

Figure 7 *Distribution of ventilation-perfusion ratio (V_A/Q) in one horse at 25 minutes of tiletamine-zolazepam anaesthesia with different premedication. At 25 minutes of anaesthesia, intrapulmonary shunt is evident in both protocols to a similar extent, but a lower arterial oxygen tension (PaO_2) and increased ventilation-perfusion mismatch (log SDQ) were noted in protocol RBZ (romifidine, butorphanol and tiletamine-zolazepam). Note the increased mismatch of ventilation and perfusion, with the broader base of the ventilation-perfusion ratio, in protocol RBZ compared to protocol ARBZ (acepromazine, romifidine, butorphanol and tiletamine-zolazepam).*

Circulation

In studies **I**, **II**, **IV** and **VI** the systemic arterial blood pressure increased during dissociative anaesthesia compared to baseline, in agreement with earlier reports on α_2-agonists and dissociative anaesthetics (Muir *et al.* 1977, 1999; Clarke *et al.* 1986; Hubbell *et al.* 1989; Wan *et al.* 1992). When acepromazine was included in the premedication there were no significant changes from baseline in SAP (**I**, **IV-VI)** or TSR (**IV**) during dissociative anaesthesia. One concern with the use of acepromazine is the development of hypotension. This is related both to the dose and route of administration, with high intravenous doses having the most pronounced effect (Parry *et al.* 1982). In the present investigation (**I**, **IV-VI)**, inclusion of acepromazine given in a low dose intramuscularly in healthy horses

prevented some of the haemodynamic fluctuations, and the mean SAP was well maintained above 70 mmHg during anaesthesia.

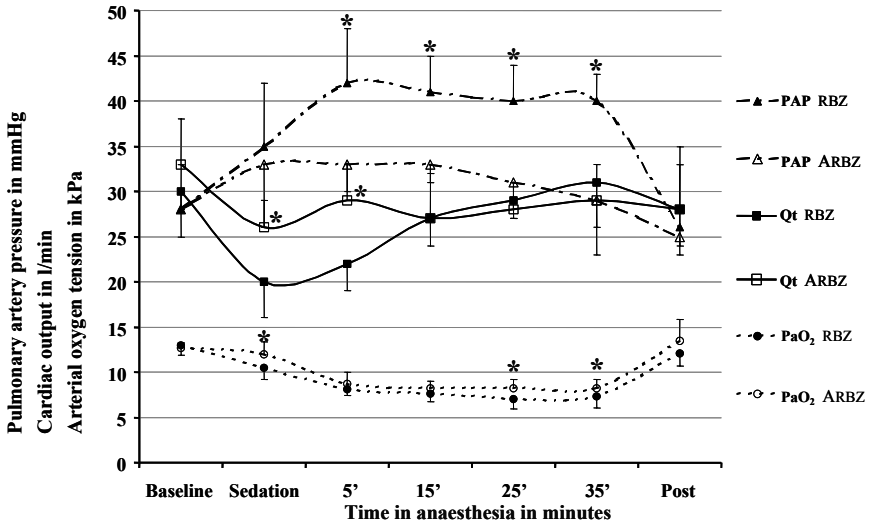

Figure 8 *Mean values ± SD (n=6) for mean pulmonary arterial pressure (PAP), cardiac output (Qt) and arterial oxygen tension (PaO_2) with different protocols. Protocol RBZ (romifidine, butorphanol and tiletamine-zolazepam), protocol ARBZ (acepromazine, romifidine, butorphanol and tiletamine-zolazepam). Significant differences in PaO_2 between protocols relate to different mechanisms during sedation and anaesthesia. During sedation a better maintained Qt preserved PaO_2 with the ARBZ protocol. During anaesthesia the increased PAP may attenuate hypoxic pulmonary vasoconstriction and disturb the matching of perfusion to ventilated areas in the lung, resulting in decreased PaO_2 with RBZ compared to ARBZ.* * *= Significant difference between protocols RBZ and ARBZ.*

Breathing air versus >95% oxygen

Because of the risk of hypoxia and myopathy during field anaesthesia, air breathing is not recommended for more than 60 minutes irrespective of the injectable drugs chosen (Matthews & Hartsfield 1993). It has been suggested that ideally one should be equipped with a tracheal tube, demand valve and oxygen cylinder when performing field anaesthesia, in order to be able to ventilate the horse for 10-20 minutes or until spontaneous ventilation returns, if apnoea occurs (Waterman *et al.* 1982; Taylor & Clarke 1999). It has also been proposed that horses under intravenous anaesthesia could be intubated and connected to a demand valve, allowing administration of oxygen and ventilation periodically to prevent atelectasis (Riebold *et al.* 1980).

The major finding in study **V** was the development of a significantly larger intrapulmonary shunt (13±5%) when the horses inspired oxygen at a high concentration compared to air breathing (5±2%) during dissociative anaesthesia. This finding is in conformity with reports from human studies that breathing of

100% oxygen during preoxygenation and anaesthesia promoted intrapulmonary shunt and atelectasis compared to breathing of 30-40% oxygen (Reber *et al.* 1996; Rothen *et al.* 1995a, 1996). In the present investigation inhalation of a high fraction of oxygen increased PaO_2, as expected, but at the same time created a significantly larger intrapulmonary shunt (Fig. 9). During air breathing in the present study the mean shunt (8% at 25 minutes) was found to be less pronounced than the mean shunt of 20% or more previously observed in anaesthetised horses in lateral recumbency in which the anaesthesia was maintained with halothane or isoflurane in oxygen (Nyman & Hedenstierna 1989; Moens *et al.* 1994). Although no direct comparison is possible, the difference might be attributable to the use of different fractions of inhaled oxygen, drug-induced differences or better preserved muscular tone, particularly the diaphragm tone, during dissociative anaesthesia. Spontaneously breathing human subjects anaesthetised with ketamine alone are reported to have well matched pulmonary ventilation and perfusion without shunt (Tokics *et al.* 1987). In the present study in horses, the dissociative anaesthetic was combined with drugs that enhance muscle relaxation (romifidine, zolazepam), and intrapulmonary shunt was evident.

A previous investigation has revealed that in the horse, increased shunt is mainly created by collapsed lung tissue (atelectasis) in the dependent part of the horse lung (Nyman *et al.* 1990). In the border area between ventilated and non-ventilated lung areas, the composition of the inhaled gas will affect the ability of the alveoli to stay open. If a lung unit is entirely closed off, the time taken for the alveoli to collapse has been estimated to be 6-9 hours if the unit contains air and about 8 minutes if it contains 100% oxygen (Joyce *et al.* 1993). After a recruitment manoeuvre in anaesthetised human patients atelectasis recurred within 5 minutes if the patients were ventilated with F_IO_2=1.0, in contrast to the group ventilated with F_IO_2=0.4, where atelectasis was eliminated for at least 40 minutes (Rothen *et al.* 1995b) Thus, in the present study the shunt may be the result of compression atelectasis due to the relaxed diaphragm tone and the recumbent position with both protocols during anaesthesia. The significantly larger shunt after breathing of >95% oxygen may be the result of transformation of intermittently closed alveoli to atelectasis by resorption of oxygen by the blood.

Return to air after high oxygen breathing

There are reports in humans showing that atelectasis and impairment of the lung function, including decreased PaO_2, persist for up to four days or more postoperatively, despite standard physiotherapy and mobilisation of the patient (Lindberg *et al.* 1992). In study **V**, in horses, the intrapulmonary shunt was still significantly larger with the O_2 protocol ten minutes after return to air breathing compared to the AIR protocol (Fig. 9), but no significant difference was found in PaO_2 between the protocols at that time. This may be explained by the presence of low V_A/Q and more mismatch between ventilation and perfusion (log SDQ) in the AIR protocol (Fig. 9). After 25 minutes of anaesthesia the V_A/Q distribution was not measured in study **V**.

In humans, inhalation of pure oxygen at the end of anaesthesia promotes postoperative atelectasis (Benoit *et al.* 2002). In horses it has been reported that the hypoxaemia that developed during anaesthesia with halothane or isoflurane in

100% oxygen persisted into recovery in lateral recumbency despite oxygen supplementation (Trim & Wan 1990). Gleed & Dobson (1988) found that PaO_2 was impaired during inhalation anaesthesia in dorsal and lateral recumbency, but PaO_2 increased rapidly when the horses were turned to sternal recumbency. Thus, it seems likely that the intrapulmonary shunt induced during inhalation of high oxygen concentrations may persist into recovery in lateral recumbency. However, the shunt may be reduced during sternal recumbency and standing. In the healthy horses in study **V**, five minutes after standing PaO_2 had returned to the baseline level and it seems unlikely that intrapulmonary shunt was present after standing. The recovery period is critical for this species and the effect of different oxygen concentrations during anaesthesia on the appearance and disappearance of intrapulmonary shunt during and after recovery needs to be investigated.

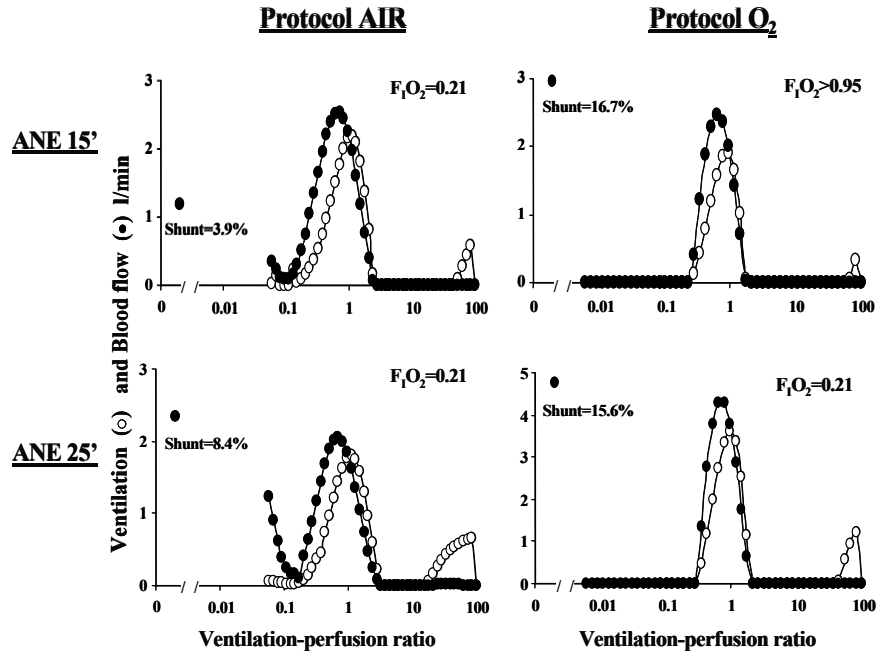

Figure 9 *Distribution of ventilation-perfusion ratio (V_A/Q) in one horse at 15 and 25 minutes of anaesthesia (ANE 15' and ANE 25'). At ANE 15' the intrapulmonary shunt was larger when the horse had breathed > 95% oxygen (protocol O_2) than when it had breathed 21% oxygen (protocol AIR). At ANE 25' the shunt introduced during O_2 breathing remained larger; this was 10 minutes after the inspired oxygen concentration was reduced to 21%, possibly indicating persistence of the resorption atelectasis produced during high O_2 breathing.*

Oxygen delivery and oxygen extraction

There was a significant difference in haemoglobin concentration between protocol RBZ and protocol ARBZ during sedation and anaesthesia (Fig. 10). The Hb was significantly increased during sedation with the RBZ protocol compared to baseline. The increase may be due to a physiological response to the decreased PaO_2 or a drug effect. However, the haemoglobin did not continue to increase concurrently with the further decrease in PaO_2 induced by anaesthesia and recumbency. Acepromazine is reported to decrease the haematocrit in horses (Ballard *et al.* 1982; Parry & Andersson 1983). The results obtained by Parry and Andersson support the theory that acepromazine causes splenic relaxation and consequent erythrocyte storage. Xylazine is reported to produce a contractile effect on the canine spleen (Hubbell & Muir 1982). It has been demonstrated that intramuscular administration of acepromazine 0.03 or 0.3 mg/kg given 15 minutes before α-agonists (e.g. adrenaline) causes an attenuation or almost complete inhibition, respectively, of the α-agonist-induced increase in haematocrit in horses (Snow 1979). Thus, the increase in haemoglobin concentration is most likely the result of a contractile effect of the α_2-agonist romifidine on the spleen. With the ARBZ protocol, acepromazine may prevent the contractile effect of romifidine and may cause splenic relaxation, with consequent erythrocyte storage.

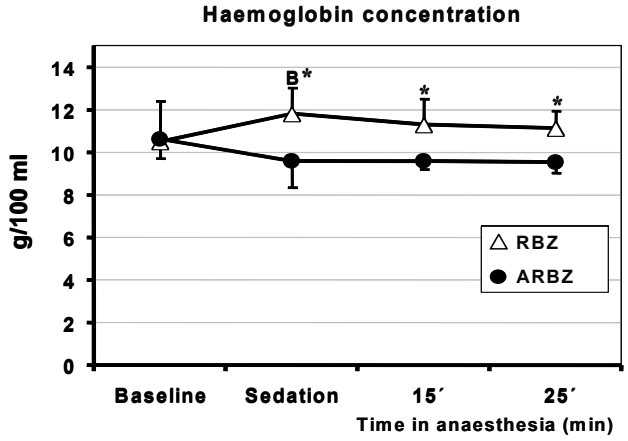

Figure 10 *Mean value ± SD (n=6) for haemoglobin concentration with protocol RBZ (romifidine, butorphanol and tiletamine-zolazepam) and protocol ARBZ (acepromazine, romifidine, butorphanol and tiletamine-zolazepam).* ***** *= Significant difference between protocol RBZ and protocol ARBZ.* ***B*** *= significant difference compared to baseline.*

A higher haemoglobin concentration implies a greater capacity of the blood to carry oxygen. Although the contractile effect of the α_2-agonist on the spleen increases the oxygen-carrying capacity of the blood in RBZ, this effect was overridden by the pronounced decrease in Qt and increase in TSR during sedation, resulting in increased oxygen extraction during sedation (Fig. 11 a and b). During the later part of the anaesthesia the arterial oxygenation was higher with ARBZ than with RBZ, although the calculated oxygen delivery was lower with ARBZ. At this time the cardiac output values were comparable and the reason for the difference in oxygen delivery would mainly be due to the difference in

haemoglobin concentration between protocols. There was no significant difference between the two protocols in calculated oxygen uptake or oxygen extraction. A slight increase in plasma lactate was observed in two horses after induction of anaesthesia (Fig. 12, own unpublished data). However, the plasma lactate decreased in these two horses during the short anaesthesia and was comparable to baseline levels at the end of anaesthesia. Muscle enzymes (ASAT) and (CK) were measured in four horses with protocols ARK, RBK, RDK, RK+K, RK+RK and RZ (own unpublished data) and were within the normal range after anaesthesia (4-6 and 2-5 µkat/l, respectively), indicating that there was no muscle damage postoperatively.

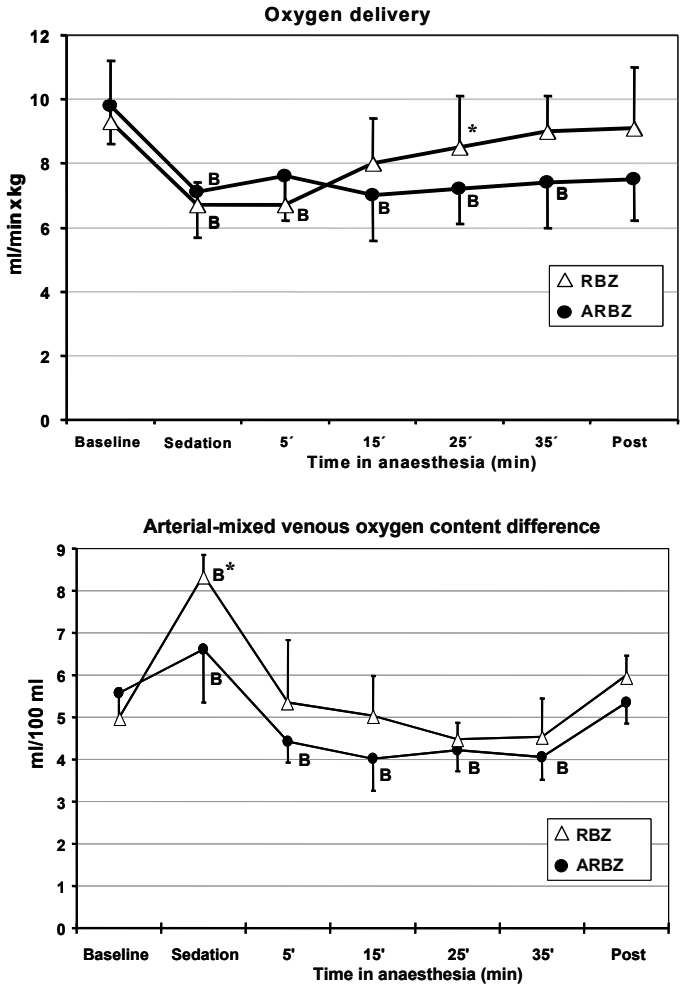

Figure 11 a and b *Mean value ± SD (n=6) for oxygen delivery and arterial-mixed venous oxygen content difference with protocols RBZ (romifidine, butorphanol and tiletamine-zolazepam) and protocol ARBZ (acepromazine, romifidine, butorphanol and tiletamine-zolazepam). * = Significant difference between protocol RBZ and protocol ARBZ.* ***B*** *= significant difference compared to baseline.*

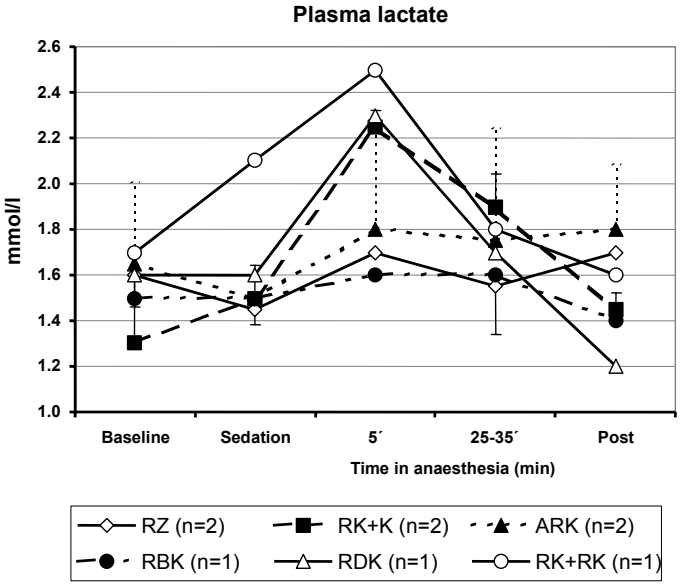

Figure 12 *Plasma lactate value in one horse with protocols RK+K, RBK and RDK, and two horses (mean±SD) with protocols RK+RK, ARK, and RZ.*

Sedation versus anaesthesia

Although the arterial oxygenation was further reduced by anaesthesia and lateral recumbency during air breathing, the oxygen delivery (Fig. 11) was not further impaired compared to that during sedation. The oxygen extraction $C(a\text{-}v)O_2$ was improved during anaesthesia compared to sedation. In study **V** a significant decrease in PvO_2 was only observed during sedation (Fig. 13). PaO_2 gives only minor information about oxygenation of the tissue. Additional information may be retrieved from PvO_2, as this is influenced by PaO_2, blood flow, oxygen extraction and consumption and blood pH. Mixed venous oxygen tension has been found to be a better predictor of hyperlactataemia and death than either arterial PaO_2 or Qt alone in critically ill human patients (Kasnitz *et al.* 1976). In an equine study by Freeman *et al.* (2002), PvO_2 was significantly decreased after romifidine sedation and the decrease persisted during the 2 hours of observations. The proposed cause of the low PvO_2 was the cardiovascular effects of the α_2-agonist including decreased cardiac output, shift in vascular resistance and blood pressure. In the present study, administration of the dissociative anaesthetic improved the circulation and PvO_2. During the entire anaesthesia with air breathing, PvO_2 was at the same level as the baseline values, indicating that the oxygen delivery to the body was sufficient to cover the overall tissue demand in these healthy horses.

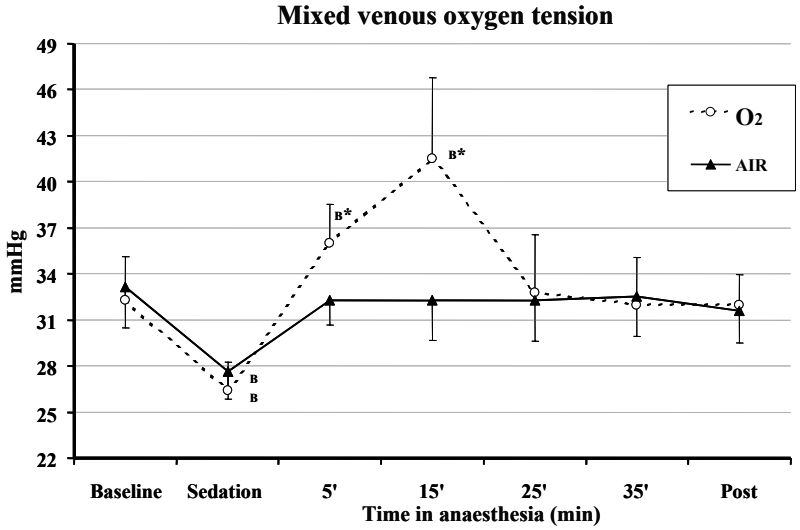

Figure 13 Mean ± SD (n = 6) values for mixed venous oxygen tension (PvO_2) during protocol ARBZ (acepromazine, romifidine, butorphanol and tiletamine-zolazepam), anaesthesia with air breathing (AIR) or F_IO_2>95% in the first 15 minutes of anaesthesia (O_2). During anaesthesia with air breathing PvO_2 was at the same level as at baseline, i.e. in the standing awake horse, indicating that the oxygen delivered was sufficient to cover the tissue demand. However, PvO_2 was significantly decreased during sedation compared to the baseline value. Inspiration of >95% oxygen (O_2) resulted in PvO_2 values in excess of those in the standing awake horse. **B** = significant difference from baseline, ***** = significant difference between protocols.

Clinical application

During the clinical investigation (study **VI**) the horses could not serve as their own controls and individual variations may have influenced comparisons between protocols. The systemic arterial blood pressure was significantly higher during protocol RZ than during the protocols including acepromazine, in accordance with findings in study **IV**. Further, the arterial oxygen tension was lowest in the group without acepromazine, although the horses in this group were on average 50 kg lighter than those in the other two groups. Hypoxaemia has long been recognised as a common and potentially hazardous side effect of anaesthesia in horses, although a link between death and hypoxaemia has not been demonstrated (Taylor 2002). The effect of non-fatal hypoxaemia is difficult to assess and the time factor may play an important role. During inhalation anaesthesia in ponies, 20 minutes of PaO_2 between 4.4 and 5.8 kPa (33-44 mm Hg) did not have any detectable deleterious effect on recovery or postoperative well-being (Taylor 1998). In an investigation by Whitehair *et al.* (1996), horses were exposed to three hours of hypoxaemia (PaO_2 6.7±0.7 [kPa 50±5 mm Hg]) during inhalation anaesthesia with isoflurane or halothane. The horses were reported to be lethargic to various degrees, with decreased appetite, after halothane anaesthesia. After isoflurane anaesthesia the horses appeared to show normal behaviour, but some had a decreased appetite.

In the present investigation with client-owned horses, a central venous catheter was not placed, but instead jugular venous blood was sampled. A comparison between PvO_2 and $PjvO_2$ during the ARBZ protocol was therefore made in horses owned by the department. During anaesthesia with ARBZ there was a good correlation between mixed venous and jugular venous oxygen tension. The RZ group showed significantly lower oxygen tension in jugular venous blood compared to the group given ARBZ, during anaesthesia. This suggests that the horses without acepromazine have an overall larger extraction of oxygen when the blood passes through the tissue. In study **V**, anaesthesia with air breathing during protocol ARBZ resulted in PvO_2 similar to the standing unsedated values, indicating that the oxygen delivery was sufficient to cover the overall tissue demand. The results of study **VI** including surgery suggest a similar situation, with sufficient oxygen delivery. With all protocols the $PjvO_2$ values were well above the values of internal jugular venous oxygen tension, 2.7 kPa (20 mmHg), reported to produce unconsciousness whatever the cause (Nunn 1993).

The analgesia was not sufficient in the RZ protocol and half of the colts in this group needed further anaesthesia to complete the surgery. The analgesia was better in the other two groups when acepromazine was included in the premedication. Acepromazine, which is without analgesic properties of its own, is reported to give significantly longer analgesia in dogs when combined with oxymorphone compared to oxymorphone alone (Barnhart *et al.* 2000). A combination of butorphanol, an opioid analgesic, and romifidine in horses is reported to reduce the reaction to touch and audiovisual stimuli more than romifidine on its own (Clarke *et al.* 1991). Further, standing sedation in horses is reported to be superior with a combination of acepromazine, xylazine and methadone compared to acepromazine and xylazine (Nilsfors *et al.* 1988). Acepromazine, but also butorphanol, may have contributed to the decreased need of additional anaesthesia in the ARBZ group during castration.

It is concluded from the castrations under hospital conditions that premedication with acepromazine and butorphanol in addition to romifidine before anaesthesia with tiletamine-zolazepam improves the anaesthesia and analgesia without having adverse effects on the cardiorespiratory function or on the quality of induction and recovery in healthy horses.

Field conditions

Since the ARBZ protocol was considered to be the most suitable for castrations under hospital conditions, it was chosen for castration of colts in field practice. As 22% needed further anaesthesia when this protocol was used at the animal hospital, it was expected that approximately 7 of the 31 colts would need further anaesthesia under field conditions. However, none of the 31 colts castrated in the field needed supplementary anaesthesia. One explanation for this result may be that the colts operated on in the animal hospital had a higher sympathetic tone before sedation and anaesthesia. The colts had previously been transported to the animal hospital, some for the first time. In this new environment they were placed in boxes within sight and hearing distance of other, unknown colts. These environmental changes may have induced a flight response in the horses. Under field conditions the colts were kept in their own environment and together with

colts of their own known herd, where a herd hierarchy was already established. Although many people were involved, the novelty stimuli during field castration may have been less pronounced than during the procedure at the animal hospital. It was our subjective impression that the sedation of the colts was deeper under field conditions, resulting in better anaesthesia and adequate analgesia for surgery.

With the ARBZ protocol there was no difference in arterial oxygen tension or carbon dioxide tension during anaesthesia between colts castrated in the animal hospital and those treated under field conditions. There was a difference in heart rate between the two groups. Yearlings are reported to have a higher heart rate than older horses (Rossdale & Wreford 1989, Visser *et al.* 2002). On average the colts in field practice were 1.5 years old and those in the animal hospital 2.5 years. As the difference in heart rate was evident at baseline, before any drug administration, the difference during anaesthesia was probably age-related.

One disadvantage of the use of a bolus dose of a dissociative anaesthetic is the individual differences in the duration of anaesthesia and the often abrupt recovery. In the case of the dissociative anaesthetic drug ketamine, it seems that recovery in the horse is mainly a result of rapid redistribution of the drug from the central compartment, which will explain the abrupt recovery often observed in the horse (Waterman *et al.* 1987). In the present investigation, with protocol ARBZ the average time spent in lateral recumbency was approximately ten minutes shorter under field conditions than during treatment at the animal hospital. This result seemed at first slightly surprising, as the anaesthesia was judged to be deeper under field conditions. The higher heart rate under field conditions may have generated a better cardiac output and thereby faster redistribution of the dissociative anaesthetic, resulting in a shorter period of anaesthesia. The anaesthesia and analgesia were sufficient for clamping of the second spermatic cord at an average time of 12.5 minutes after induction, which allowed inexperienced surgeons enough time to perform the castration procedure under field conditions. However, veterinarians planning to use this anaesthetic protocol in field practice must take into consideration the individual variation in the time spent in lateral recumbency, in this study 30-70 minutes. The time from completion of surgery to return of the horse to the standing position was unnecessarily long in many cases. Other drug combinations and/or other relative proportions of dissociative anaesthetic and benzodiazepine might result in anaesthesia sufficient for castration and with a shorter recovery time. Prolongation of the anaesthesia was not necessary under field conditions. The recommendation to avoid field anaesthesia lasting more than 60 minutes without a possibility of giving supplementary oxygen (Matthews & Hartsfield 1993) is still accepted, but further research is of interest in this area. As with all dissociative anaesthesia in horses, prerequisites for a successful result are deep sedation, undisturbed time after induction, proper positioning to avoid muscle ischaemia, and unforced recovery.

In summary, the clinical study showed that under hospital conditions some horses, with all three anaesthetic protocols, needed supplementary anaesthesia to complete surgery. Tiletamine-zolazepam anaesthesia, after premedication with acepromazine, romifidine and butorphanol, provided sufficient anaesthesia for castration 5-20 minutes after induction under field conditions. Cardiorespiratory

changes were within acceptable limits in these clinically healthy colts with normal haemoglobin concentrations. The quality of induction and recovery were good.

Summary and suggested future research

In total, in these studies we have given 117 dissociative anaesthesias in horses, without any major complications or mortality. All inductions, anaesthesias and recoveries have been calm without excitation. The addition of diazepam or zolazepam resulted in earlier muscle relaxation, and with these drugs a tail holder may therefore be advisable during the induction. In most cases a standing position was achieved at the first attempt and only two horses needed more than one attempt. Tiletamine-zolazepam anaesthesia, after premedication with acepromazine, romifidine and butorphanol, proved to be suitable for castration of colts in a teaching situation under field conditions. However, at the animal hospital there was a need for supplementary anaesthesia to complete surgery in some of the cases. Cardiorespiratory changes were within acceptable limits during air breathing in these clinically healthy colts.

Future research

The anaesthesia after sedation with acepromazine, romifidine and butorphanol followed by tiletamine-zolazepam was reliable but sometimes the time in recumbency was unnecessarily long. Further investigations with replacement of tiletamine-zolazepam by ketamine and diazepam but with inclusion of acepromazine and butorphanol would be of interest.

One of the major findings during anaesthesia was the development of a significantly larger intrapulmonary shunt when the horses breathed high oxygen concentrations compared to air breathing. The impact of the proposed resorption atelectasis may be more pronounced during longer inhalation anaesthesia. Cuvelliez *et al.* (1990) reported that horses breathing 85% oxygen during 4 hours of inhalation anaesthesia displayed increased carbon dioxide retention and a progressive increase in the alveolar–arterial oxygen partial pressure difference, compared to the situation when the horses breathed 30% oxygen. In humans preoxygenation with 100% oxygen increased early formation of atelectasis compared to preoxygenation with 80% oxygen or less (Edmark *et al.* 2003). The optimal inspired oxygen concentration during anaesthesia and its effect on the critical recovery period is not known in the horse and further studies are needed in this area.

Conclusions

1. Additional premedication with butorphanol or diazepam did not alter the cardiorespiratory response to romifidine and ketamine, while acepromazine maintained the studied circulatory parameters closer to the standing unsedated values. Acepromazine and diazepam improved the quality of induction and anaesthesia.

2. No significant differences in cardiorespiratory parameters were found between romifidine/tiletamine-zolazepam anaesthesia and prolonged anaesthesia with romifidine/ketamine. However, prolongation with ketamine alone provided a poor quality of anaesthesia.

3. The observed decrease in arterial oxygenation during sedation with α_2-agonists was manly attributed to a reduced cardiac output and increased V_A/Q mismatch. During dissociative anaesthesia cardiac output was improved, but arterial oxygenation was further impaired, as a result of increased intrapulmonary shunt and mismatch. Addition of acepromazine to the sedation with romifidine and butorphanol resulted in better maintenance of circulation and arterial oxygenation both during sedation and during dissociative anaesthesia. Although the arterial oxygenation was further impaired by anaesthesia and recumbency compared to that during sedation, the oxygen delivery did not decrease further. The arterial-mixed venous oxygen content difference and mixed venous oxygen tension remained closer to the standing unsedated values during anaesthesia than during sedation.

4. Breathing more than 95 % oxygen during dissociative anaesthesia improved arterial oxygenation compared to air breathing, but concomitantly increased intrapulmonary shunt and introduced hypoventilation. The intrapulmonary shunt created during anaesthesia with high oxygen concentrations persisted when the horses returned to air breathing, possibly indicating that resorption atelectasis produced during high oxygen breathing subsequently persisted during anaesthesia and recumbency.

5. Tiletamine-zolazepam anaesthesia, after premedication with acepromazine, romifidine and butorphanol, proved to be suitable for castration of colts under field conditions. Under hospital conditions there was a need for supplementary anaesthesia to complete surgery in some cases. Cardiorespiratory changes were within acceptable limits during air breathing in these clinically healthy colts.

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