Observations on the use of midazolam for sedation, and induction of anaesthesia with midazolam in combination with ketamine in the goat

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ABSTRACT

Midazolam hydrochloride administered intramuscularly at a dosage of 0.4 mg/kg induced sedation and sternal recumbency in goats. Increasing the dosage to 1 mg/kg resulted in rapid onset of ataxia followed by lateral recumbency, and loss of consciousness. Light surgical anaesthesia lasted for a period of 7–15 min and was suitable for non-painful procedures. Heart rate was significantly increased ($p < 0.05$) at both dosage rates, while respiration rate was only increased after midazolam at 0.4 mg/kg. The combination of midazolam (0.4 mg/kg) and ketamine hydrochloride (4 mg/kg) increased heart and respiration rate significantly ($p < 0.05$). A light plane of surgical anaesthesia suitable for endotracheal intubation was induced, which lasted for a period of 16–39 min.

Key words: anaesthesia, caprine, immobilisation, ketamine, midazolam, sedation.

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INTRODUCTION

The combination of xylazine hydrochloride and ketamine hydrochloride is commonly used for induction of anaesthesia in small ruminants. Ketamine may not be suitable on its own for general anaesthesia owing to increased muscle tone and insufficient analgesia for surgical procedures[12]. Xylazine is co-administered to obtain surgical anaesthesia but may result in pulmonary oedema in sheep[15]. Alternatively, diazepam may be used[2]. The combination of diazepam and ketamine is recommended for use in old or debilitated animals[5]. Midazolam hydrochloride belongs to the benzodiazepine group of drugs, and in comparison to diazepam it is 4 times more potent. In addition, it is water-soluble, which makes it more suitable for intramuscular administration. The purpose of this study was to investigate the clinical effects of midazolam administered intramuscularly in goats, and its suitability as an adjunct to ketamine anaesthesia.

MATERIALS AND METHODS

General anaesthesia was required for subcutaneous relocation of the carotid artery in a group of 7 neutered male goats with body mass ranging from 18 to 26.6 kg. The protocol for this investigation was approved by the Ethical Committee of the Faculty of Veterinary Science, University of Pretoria.

All the animals were deprived of food and water for 18 h before sedation or anaesthesia. For induction of anaesthesia, the goats were premedicated with midazolam hydrochloride (Dormicum, Roche) injected intramuscularly at a dosage of 0.4 mg/kg body mass. This route was selected for its ease of administration during induction of anaesthesia, thus avoiding physical immobilisation. After the animals became recumbent, they were restrained in left-lateral recumbency and an 18G catheter (Jelco, Critikon) introduced into the median vein on the medial aspect of the carpus. Anaesthesia was induced by intravenous administration of ketamine hydrochloride (Anaket, Centaur) at a dosage of 4 mg/kg body mass. After loss of consciousness, an endotracheal tube was placed with the aid of a laryngoscope. The skin over the right jugular groove was surgically prepared. As soon as the 1st sign of recovery appeared, such as movement, the endotracheal tube was connected to a circle inhalation anaesthetic machine. Anaesthesia was maintained with halothane (Fluothane, Zeneca) in oxygen with the vaporiser setting at 2 % during surgery. For removal of the cutaneous sutures 14 days after surgery, the goats were immobilised with 1 mg/kg body mass of midazolam injected intramuscularly.

Heart and respiratory rates were recorded before each treatment. For midazolam at 0.4 mg/kg, heart and respiratory rates were recorded immediately after adoption of sternal recumbency, and at 1 mg/kg after adoption of lateral recumbency. The time required for recovery to sternal recumbency and standing were recorded. For the midazolam/ketamine combination the time to the 1st sign of recovery was recorded. To evaluate sedation, the animals were observed for ataxia and lowering of the head and neck. The scoring for sedation and anaesthesia is summarised in Table 1. The depth of anaesthesia was evaluated according to eyeball rotation and the palpebral reflex; muscle relaxation was judged by jaw muscle tone; and analgesia by the hind limb withdrawal reflex elicited by pressing a pencil point on the coronary band of the claw for a period of 15 sec (Table 1). Any other clinical effects were also recorded.

Analysis of data

Heart and respiratory rates were recorded as mean (±SD), and recumbency and recovery times (min) as mean, maximum and minimum, and analysed with 1-way analysis of variance for repeated measures. If a significant difference was found within treatment groups, the Tukey test was applied. Significance was accepted at the 95 % confidence level. The Sigmastat 2 software programme (Jandel Corporation, San Rafael) for a personal computer was used for statistical analysis.

RESULTS

Sedation with midazolam

The heart and respiration rates after the administration of midazolam are summarised in Table 2. Midazolam at 0.4 mg/kg increased both mean respiration and heart rate significantly from 20 (±9) to 27 (±9) breaths/min and 60 (±3) to 75 (±12)

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beats/min respectively ($p < 0.05$). Similarly, at 1 mg/kg the heart rate increased significantly from 74 (±12) to 103 (±19) beats/min ($p < 0.05$). The respiration rate remained unaltered at 28 breaths/min.

The mean time for midazolam to induce recumbency, and for recovery are shown in Table 3. Sedation with midazolam (0.4 mg/kg) was characterised by lowering of the head and neck and ataxia in all animals within 5 (range 3–7) min. Sternal recumbency followed within 16 (8–35) min. The goats remained conscious and were able to stand when disturbed. Very little salivation was observed during this period. After midazolam (0.4 mg/kg) the score for sedation was 100 %. When midazolam was administered at 1 mg/kg, sedation was observed within 2.7 (1–4) min and followed by sternal recumbency. Lateral recumbency and loss of consciousness followed in 11.2 (7–18) min. The score for eyeball rotation was 86 %, palpebral reflex depression 71 %, jaw muscle tone 86 %, and limb withdrawal reflex depression (analgesia) 33 % (Table 1). Midazolam failed to induce lateral recumbency and loss of consciousness in 1 goat. An opisthotonos-like effect with extension of the head and neck was noted in 4 of the animals during lateral recumbency. Time required for recovery from lateral to sternal recumbency was 18 (8–30) min, and to standing (from lateral recumbency) 49.7 (17–69) min (Table 3). Neither bloat nor regurgitation was observed. Recovery was uneventful, and the goats commenced feeding immediately after standing recovery. One goat began to eat while in sternal recumbency.

Table 1: **Scoring for sedation and anaesthesia after midazolam.**

	Score	Number of animals	Total score
Sedation			
Ataxia	1	7	
Head and neck lowering	1	7	14/14 = 100 %
Eye ball rotation			
Central	1	2	
Down	2	5	12/14 = 86 %
Palpebral reflex			
Brisk	1	2	
Depressed	2	2	
Absent	3	3	15/21 = 71 %
Jaw muscle tone			
Chew	1	1	
Resistance	2	1	
Relaxed	3	5	18/21 = 86 %
Limb withdrawal			
Active	1	7	
Depressed	2	0	
Absent	3	0	7/21 = 33 %

Table 2: **Heart and respiration rates after intramuscular administration of midazolam and ketamine** (mg/kg).

	Dose (mg/kg)	Mean HR[a] (SD[c])	Mean RR[b] (SD)
Pretreatment		60 (3)	20 (9)
Midazolam	0.4	75[d] (11)	27[f] (9)
Ketamine	4	106[e] (13)	43[g] (15)
Pretreatment		74 (12)	28 (11)
Midazolam	1	103[h] (19)	28 (6)

[a]RR = respiration rate (breaths/min).
[b]HR = heart rate (beats/min).
[c]SD = standard deviation.
[d-h]Statistically significant ($p < 0.05$) increase after administration of: (d) midazolam; (e) ketamine; (f) midazolam; (g) ketamine; (h) midazolam.

Induction of anaesthesia with midazolam/ketamine combination

Following sedation with midazolam (0.4 mg/kg), the administration of ketamine increased the heart rate significantly ($p < 0.05$) from 75 (±11) to 106 (±13) beats per minute (Table 2). Consciousness was lost in all animals, with the eyeballs rotated downwards. All animals were successfully intubated. Average duration of anaesthesia was 13.4 (8–21) min, after which signs of recovery, such as swallowing, tail flicking or head movement, appeared. Mild salivation was observed in all goats after ketamine administration. Neither bloat nor regurgitation was observed. Recovery from the halothane anaesthesia after surgery was uneventful.

Table 3: **Time** (min; mean, minimum and maximum**) required for midazolam to induce sedation, lateral recumbency, recovery into sternal recumbency and standing; and recovery after midazolam/ketamine.**

	Mean	Minimum	Maximum
Midazolam sedation			
0.4 mg/kg	5	3	7
1 mg/kg	2.7	1	4
Midazolam induction			
0.4 mg/kg – sternal recumbency	16	8	35
1.0 mg/kg – lateral recumbency	11.2	7	18
Midazolam recovery			
1 mg/kg – sternal recumbency	18	8	30
1 mg/kg – standing (from lateral recumbency)	49.7	17	69
Midazolam/ketamine recovery	13.4	8	21

DISCUSSION

Use of the benzodiazepine diazepam for sedation and anaesthesia in production animals such as calves, adult cattle, sheep, goats and pigs has been reported[1,10,11,14]. No clinical report on the use of midazolam for sedation or as an adjunct to anaesthesia in goats is currently available. Diazepam will provide up to 30 min of sedation in goats[12]. It is recommended that diazepam be administered slowly intravenously at 0.25–0.5 mg/kg for restraint in minor surgical procedures in ruminants. In calves, sufficient sedation and muscle

relaxation with diazepam are obtained at 0.4 mg/kg[10]. In this investigation, midazolam (0.4 mg/kg) induced reliable sedation after intramuscular administration, and may be suitable as premedication before induction of anaesthesia. Additional restraint was required for a procedure such as venipuncture. Increasing the dosage of midazolam to 1 mg/kg rapidly induced lateral recumbency and loss of consciousness sufficient to allow the removal of sutures without additional physical restraint. The goats appeared to be in a state of deep hypnosis or light surgical anaesthesia, as the palpebral reflex was absent and the eyeballs rotated downwards. The limb withdrawal reflex elicited by a noxious stimulus remained active. Midazolam does not have analgesic effects in humans but it decreases the minimum alveolar concentration for halothane by at least 30 %[9]. Endotracheal intubation was not attempted at this stage. The dose-dependent effect of midazolam observed in the goat, ranging from sedation to light anaesthesia, was similar to the clinical effects seen in humans. The cause of the extension of the head and neck observed in this investigation is unknown. Palpation of the muscles around the neck did not indicate any increased muscle tone, and manual flexion of the atlanto-occipital joint did not reveal any abnormality. It is possible that the neck muscles, relaxed by midazolam, could not counter the passive tension of the elastic *ligamentum nuchae.* In contrast to the findings of this study, profuse salivation was observed in sheep after intravenous administration of midazolam at 0.3 mg/kg[7].

The increase in heart rate observed in this investigation was similar to the effect of diazepam in ruminants and pigs[10,14]. Potentially adverse effects may result from midazolam despite the modest cardiovascular effects reported for the benzodiazepines. The baroreflex may be preserved and a decrease in blood pressure may result in an increase in heart rate. Midazolam is reported to be more hypotensive than diazepam. In humans, at a dosage of 0.2 mg/kg, the hypotension is similar to that induced by thiopentone at 4 mg/kg. The haemodynamic effects are dose-related but a ceiling effect exists above which additional doses do not increase cardiovascular side-effects. The hypotensive effect is only transient[8]. In the pig, midazolam decreases heart rate[14]. In the calf, the arterial blood pressure is not influenced by diazepam. Other possible adverse effects reported are tachycardia, arterial hypoxaemia and an increase in the oxygen extraction ratio. Fast intravenous injection produces respiratory distress, whereas intramuscular injection of diazepam produces muscle rigidity and inadequate sedation[10].

Sedation and anaesthesia followed rapidly after the intramuscular administration of midazolam, except for one goat in which only sedation and sternal recumbency were obtained after 1 mg/kg. An erroneous injection into facial planes, resulting in delayed absorption, may have caused this deviation. The intramuscular route is convenient for sedation or immobilisation of small stock, especially if an anaesthetic depth sufficient for intubation can be obtained without compromising patient safety. Combination with ketamine may afford this option.

Respiration rate increased in the goat at the lower midazolam dosage (0.4 mg/kg), but remained unaltered at the higher dosage of 1 mg/kg. By contrast, the respiration rate in the pig is decreased at 0.1 mg/kg[14]. In humans the central respiratory drive is decreased by midazolam at 0.15 mg/kg[4]. Observations on cardiopulmonary variables such as blood pressure, arterial blood-gas analysis, tidal and minute volume are required for the interpretation of variables such as heart and respiration rate, but were outside the scope of this investigation.

Both diazepam and midazolam belong to the benzodiazepine group of drugs that exert their effects by occupying the benzodiazepine receptor and facilitating the inhibitory action of gamma-aminobutyric acid on postsynaptic transmission. Other clinical effects include anticonvulsive activity and centrally mediated muscle relaxation. The anxiolytic and muscle-relaxing activities are associated with an increase in the inhibitory neurotransmitter glycine within the spinal cord and in certain brain centres. The benzodiazepines protect the brain against hypoxia and increase the threshold for seizures[3]. The appetite-stimulating effect of the benzodiazepines has been reported previously[16] in the goat and a corresponding reaction to food was seen immediately after recovery from midazolam. Diazepam is highly lipid-soluble but insoluble in water and the commercial parenteral preparation for diazepam (Valium, Roche) requires the use of a lipoidal solvent propylene glycol (40 %) and ethyl alcohol (10 %), which may result in venous irritation and pain on injection. By contrast, the commercial preparation of midazolam maleate (Dormicum, Roche) is water-soluble when buffered at a pH of 3.5. When administered parenterally the drug becomes highly lipid-soluble at physiological pH, which is responsible for its rapid onset of action[3].

Ketamine hydrochloride is a water-soluble salt that may be administered by the intramuscular or intravenous route. When administered on its own it produces a cataleptic state whereby the animal is immobilised and the righting reflex lost. It is also known as a dissociative anaesthetic as result of the electroencephalographic evidence of the dissociation between thalamus and limbic system. Ketamine stimulates the sympathetic nervous system, producing an increased heart rate. Peripheral vascular resistance is minimally affected as result of its direct vasodilatory effect and sympathetically mediated vasoconstriction in the peripheral vasculature[13]. Muscle tone is increased and may also be associated with tonic-clonic spasms or even convulsions in the dog[6]. On its own, ketamine causes opisthotonos, trembling and jaw champing in the ruminant[5]. To be able to use ketamine for induction of anaesthesia and allow endotracheal intubation, an adjunct must be added to improve muscle relaxation. The dosage for ketamine varies depending on the clinical effect required and the adjunct used. Coulson *et al*[2] used ketamine at 7.5 mg/kg in combination with diazepam at 0.375 mg/kg in sheep. Riebold[11] recommends the dose for ketamine at 4.4 mg/kg along with diazepam at 0.1 mg/kg. The benzodiazepine dosages recommended for sheep and goats are similar. The anaesthetic depth after the administration of midazolam (0.04 mg/kg)/ketamine (4 mg/kg) was similar to that observed with midazolam at a dose of 1 mg/kg. The potential to obtain surgical anaesthesia with midazolam on its own is less than the midazolam/ketamine combination, as midazolam is a poor analgesic in comparison to ketamine.

In conclusion, midazolam administered intramuscularly at a dosage of 0.4 mg/kg induced sedation within 3–7 min. Increasing the dosage to 1 mg/kg provides rapid loss of consciousness and muscle relaxation within 7–18 min in the goat. Combining midazolam at 0.4 mg/kg with ketamine hydrochloride at 4 mg/kg induced light surgical anaesthesia suitable for endotracheal intubation.

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