Acta vet. scand. 1998, *39,* 127-134.

Medetomidine-Midazolam Sedation in Sheep

By *M. Raekallio, R-M. Tulamo* and *T. Valtamo*

Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Helsinki, Finland.

Raekallio M, Tulamo R-M, Valtamo T: Medetomidine-midazolam sedation in sheep. Acta vet. scand. 1998, 39, 127-134. – Seven sheep were sedated 3 times: with medetomidine (15 μg kg^{-1}), with midazolam (0.1 mg kg^{-1}) and with a combination of the drugs. All drugs were administered intravenously. Heart and respiratory rates were measured. Arterial blood samples were collected, and PaO_2, $PaCO_2$, pH, haemoglobin concentration and saturation, and base excess were determined. Systolic and mean arterial pressures were recorded before and after the treatment with medetomidine-midazolam.

Midazolam increased the time of recumbency induced by medetomidine. After administration of midazolam alone, 4 of the 7 sheep were sedated and the other 3 were excited. Heart rate decreased after both medetomidine and medetomidine-midazolam. One sheep suffered a cardiac arrest after medetomidine-midazolam injection, and it required resuscitation. PaO_2 and haemoglobin oxygen saturation decreased after medetomidine, and medetomidine-midazolam caused a marked hypoxaemia. $PaCO_2$ increased after medetomidine, both alone and combined with midazolam, but arterial pH was within the reference values after all drug administrations. Systolic and mean arterial pressures decreased after medetomidine-midazolam.

This study indicates that though in sheep midazolam potentiates the sedative effect of medetomidine, the combination of medetomidine and midazolam also reduces the in PaO_2 and haemoglobin oxygen saturation more than medetomidine alone. The results indicate that a medetomidine-midazolam combination is unsafe for sheep at the doses studied.

hypoxaemia; excitation; sheep.

Introduction

Midazolam in the sheep produces antinociception, which is probably mediated by a specific interaction with the $GABA_A$/benzodiazepine receptor complex (*Kyles et al.* 1995). It is also used for the induction of anaesthesia in humans (*Michaloudis et al.* 1995). A combination of medetomidine and midazolam has a potent sedative effect, which is most likely due to a synergistic interaction between these drugs, in rats (*Salonen et al.* 1992), pigs (*Nishimura et al.* 1993) and dogs (*Hayasi et al.* 1994). Thus, midazolam might potentiate the sedative effects of medetomidine when used in combination with medetomidine in sheep.

A combination of medetomidine and ketamine has been used to anaesthetize sheep (*Laitinen* 1990), but this combination is not optimal, because it is known to cause marked hypoxemia (*Tulamo et al.* 1995) in a similar manner as medetomidine alone in sheep (*Alibhai et al.* 1993). In dogs, the dose of medetomidine can be reduced when it is combined with midazolam. This treatment has been reported to reduce the adverse effect of medetomidine, especially

in peripheral vasoconstriction (*Hayashi et al.* 1995). The purpose of our study was to investigate the arterial oxygenation and haemoglobin oxygen saturation in sheep after treatment with a low dose of medetomidine combined with midazolam. The effects of the combination of medetomidine and midazolam were compared to those achieved with each of the drugs when used alone.

Materials and methods

Seven female Finnish landrace sheep, aged approximately one year, weighting 42 to 72 kg (mean 58.4 kg), were used in the study. The right carotid artery of each sheep had been transferred to a subcutaneous position several months prior to the first experiment (*Dueck et al.* 1982). The sheep were sedated 3 times: with medetomidine (15 μg kg^{-1}), with midazolam (0.1 mg kg), and with medetomidine (15 μg kg^{-1}) followed immediately by midazolam (0.1 mg/kg). All the drugs were administered via a catheter into the jugular vein. At least 7 days were allowed to elapse between the treatments. Food was withheld for 24 h prior to the experiments, but the sheep had free access to water. The sheep were intubated after administration of medetomidine with midazolam, but not after the other treatments. They were placed on their left flank if they sustained lateral recumbency, because the right carotic artery was cannulated. Heart rate was recorded by ECG and auscultation and respiratory rate by auscultation or looking at the movements of thorax before the agents were administered and 5, 10, 20, 30, 40, 50 and 60 min thereafter.

Blood samples were collected by arterial puncture from the carotid artery before the injection, and from the catheter or by puncture, 5 min, 10 min and every 10 min thereafter until 60 min. The arterial blood samples were analyzed immediately with an auto-analyzer (ABL 300, Radiometer, Copenhagen, Denmark). Arterial CO_2 and O_2 tensions, pH, haemoglobin concentration and saturation, and base excess were determined. All the parameters were followed for only 30 min after midazolam injection alone.

Arterial blood pressure was determined only in the trial with medetomidine-midazolam combination, using a catheter in the right carotid artery, with a strain gauge blood pressure transducer (LifeScope 6, Nihon Kohden, Tokyo, Japan). The zero-point for the blood pressure transducer was regulated at the level of the base of the heart. Systolic and mean arterial pressures were recorded before the induction of the anaesthesia, at 5 min and 10 min postinduction and every 10 min thereafter until 60 min.

The data were analyzed using an analysis of variance for repeated measures. If differences were present, Dunnett's two-tailed *t* test was used to compare individual time points with "before treatment" level and Student's *t* test was used to compare the treatments with each other at a certain time point. The Wilcoxon Rank Test was used to compare data that were not normally distributed (recovery times). Minimum statistical significance was taken as $p<0.05$.

Results

All the sheep assumed lateral recumbency after medetomidine and medetomidine-midazolam injections. They rose to standing position 63 min (median; lower and upper quartile 62.5 and 80 min) after the medetomidine-midazolam combination, which was significantly later ($p = 0.023$) than after medetomidine alone (median 45 min, lower and upper quartile 35 and 57 min). After administration of midazolam alone, 3 sheep lay down, 1 seemed to be sedated and ataxic and the other 3 were excited. All the sheep could be intubated shortly after the medetomidine-midazolam injection, although many

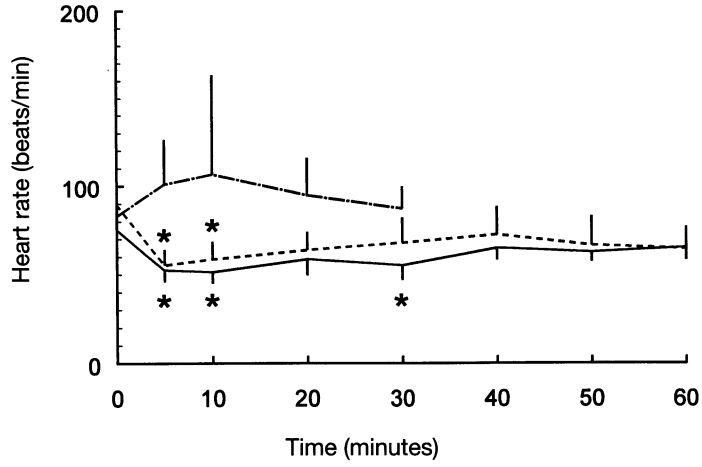

Figure 1. Heart rates (mean +/– STD) in sheep given medetomidine 15 μg kg^{-1} IV (———), midazolam 0.1 mg/kg IV (– · – · –) and the combination of medetomidine 15 μg kg^{-1} and midazolam 0.1 mg kg^{-1} IV (- - - -) (n = 7). Time point 0 indicates base line before sedation.
* Significantly different from baseline ($p<0.05$).
\+ Significant difference between medetomidine-midazolam combination and medetomidine alone ($p<0.05$).

of them had some laryngeal spasm and some were able to swallow. After the other treatments, we did not try to intubate the sheep, as the onset of sedation was slow or the sheep were not sedated at all.

Heart rate decreased after both medetomidine and medetomidine-midazolam (Fig. 1). Respiratory rate initially increased after medetomidine-midazolam injection. The increase was statistically significant only at 10 min after injection, after which it gradually returned to baseline (Fig. 2). One sheep suffered a cardiac arrest shortly after the medetomidine-midazolam injection (no detectable ECG and blood pressure were present) and again 64 min after it, and it required resuscitation; consequently the 5 min values from this individual were discarded.

Arterial O_2 tension and haemoglobin saturation decreased after the medetomidine injection and medetomidine-midazolam combination caused a marked hypoxaemia (Figs. 3 and 4). After medetomidine-midazolam 2 sheep had PaO_2 less than 5 kPa throughout the whole follow-up period and one at 5 min and 10 min. Arterial CO_2 tension increased after medetomidine, both alone and combined with midazolam (Fig. 5). Arterial pH was within the reference values (*Kaneko* 1989) after all drug administrations, and there were not any statistically significant differences between treatments. Haemoglobin concentration gradually decreased and base excess increased after medetomidine, both alone and in combination with midazolam (data not shown).

Systolic and mean arterial pressures decreased gradually after medetomidine-midazolam injection. The decrease was statistically significant when compared to the "before treatment" pressures, from 10 min after injection until the end of the follow up period (Fig. 6).

Discussion

In our study medetomidine alone caused deep

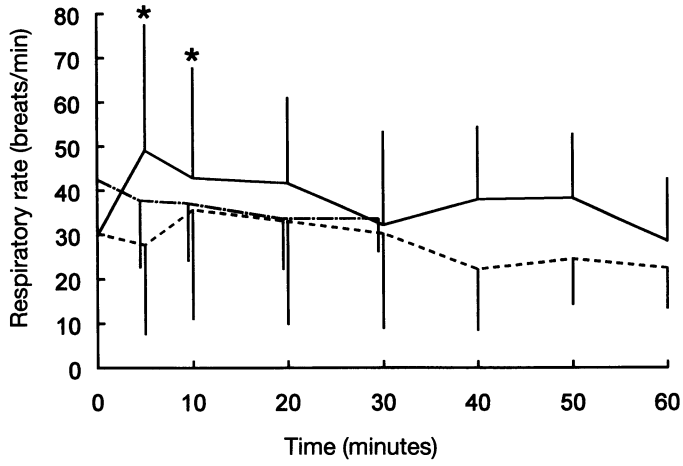

Figure 2. Respiratory rates (mean +/– STD) in sheep given medetomidine 15 μg kg^{-1} IV (——), midazolam 0.1 mg kg^{-1} IV (– · – · –) and the combination of medetomidine 15 μg kg^{-1} and midazolam 0.1 mg kg^{-1} IV (- - - -) (n = 7). (For abbreviations see Fig. 1.)

sedation and recumbency in sheep as described by *Alibhai et al.* (1993), in spite of the fact that the dose of medetomidine was slightly smaller in our study (15 μg kg^{-1}) than in the study of *Alibhai et al.* (1993) (20 μg kg^{-1}). Midazolam potentiated the sedative effect of medetomidine by increasing the time of recumbency. It was also possible to intubate the sheep after medetomidine-midazolam, which indicated a rather deep level of sedation, as intubation is consid-

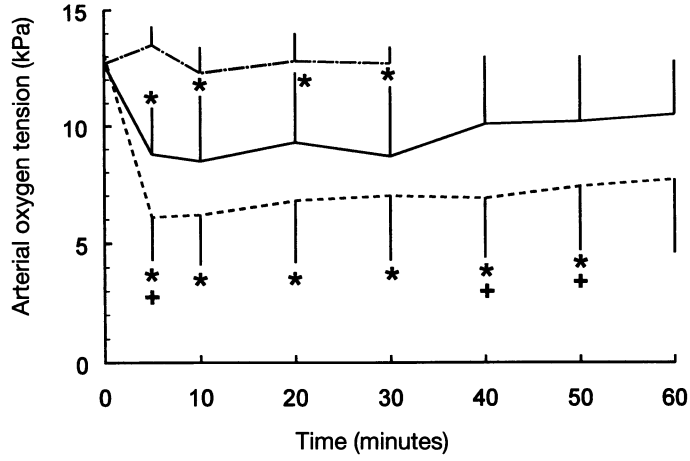

Figure 3. PaO_2 in sheep given medetomidine 15 μg kg^{-1} IV (———), midazolam 0.1 mg kg IV (– · – · –) and the combination of medetomidine 15 μg kg^{-1} and midazolam 0.1 mg kg^{-1} IV (- - - -) (n = 7). (For abbreviations see Fig. 1.)

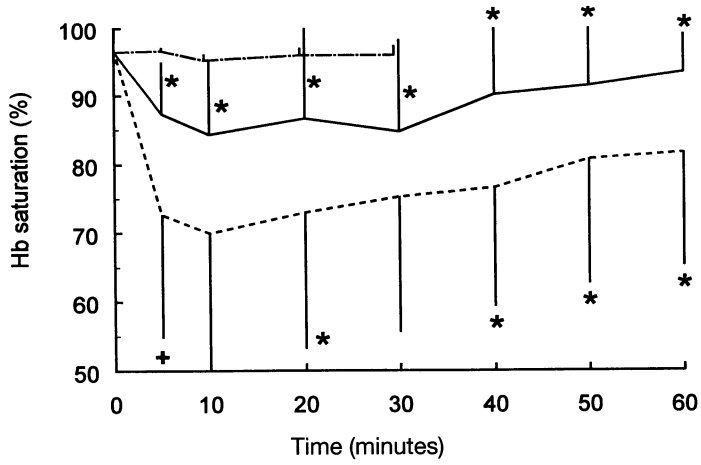

Figure 4. Oxygen saturation of haemoglobin in sheep given medetomidine 15 μg kg^{-1} IV (———), midazolam 0.1 mg kg^{-1} IV (– · – · –) and the combination of medetomidine 15 μg kg^{-1} and midazolam 0.1 mg kg^{-1} IV (- - - -) (n = 7). (For abbreviations see Fig. 1.)

ered to be a relatively strong stimulus in sheep. This potentiated effect was similar to those reported earlier in rats (*Salonen et al.* 1992), pigs (*Nishimura et al.* 1993a) and dogs (*Hayasi et al.* 1994). Some of the sheep were sedated and the others were excited after midazolam injection, which does not agree with the report of *Kyles et al.* (1995) where midazolam produced marked sedation in all the sheep tested. In our study, the sheep were taken into a different room before

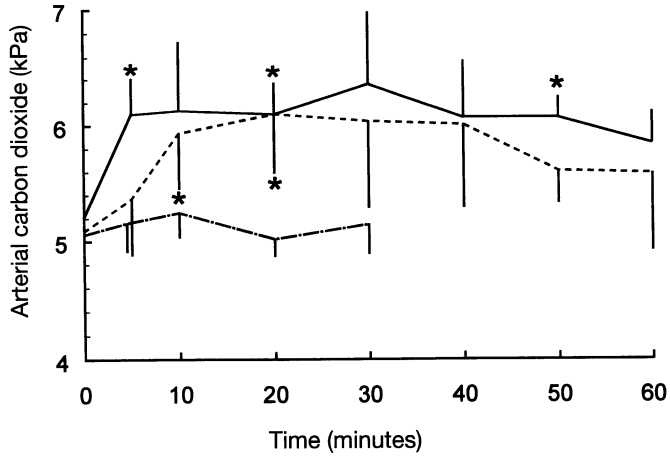

Figure 5. $PaCO_2$ in sheep given medetomidine 15 μg kg^{-1} IV (———), midazolam 0.1 mg kg^{-1} IV (– · – · –) and the combination of medetomidine 15 μg kg^{-1} and midazolam 0.1 mg kg^{-1} IV (- - - -) (n = 7). (For abbreviations see Fig. 1.)

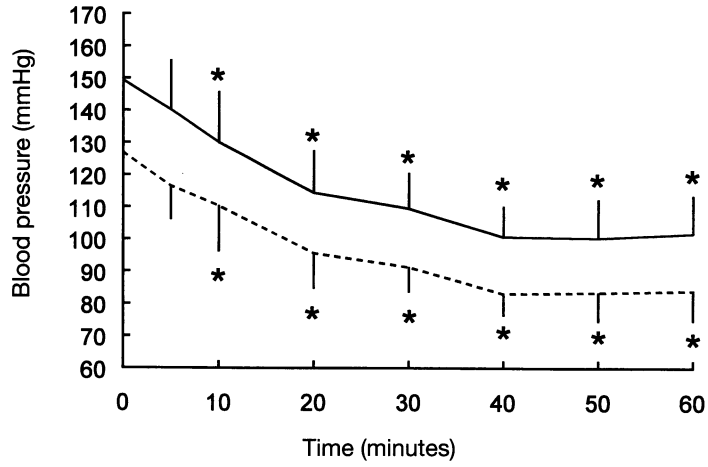

Figure 6. Systolic (———) and mean (- - - -) arterial blood pressures in sheep given the combination of medetomidine 15 $\mu g\ kg^{-1}$ and midazolam 0.1 mg kg^{-1} IV (n = 7). (For abbreviations see Fig. 1.)

treatment, which may have made them slightly excited, whereas in the study of *Kyles et al.* (1995) they were kept in the same environment. Midazolam is reported to cause restlessness and hyperactivity in some cats (*Ilkiw et al.* 1991), and ataxia and struggling before sedation in pigs (*Nishimura et al.* 1993b).

The decrease in heart rate and increase in arterial CO_2 tension after the medetomidine-midazolam combination were similar to those detected after medetomidine alone in sheep. Arterial blood pressure decreased gradually after the medetomidine-midazolam injection, but it was not critically low, except in one sheep during cardiac arrest; i.e. the lowest mean arterial pressure measured in any of the other sheep was 70 mmHg. In laboratory pigs, the intramuscular administration of medetomidine-midazolam had minimal cardiopulmonary effects (*Nishimura et al.* 1994). In dogs, the same drug combination caused transient mild pressor response, bradycardia and a decrease in cardiac index corresponding to the decrease in heart rate, and the effects on the respiratory function were slight (*Hayashi et al.* 1995). However, in our study midazolam potentiated the decrease in arterial O_2 tension and haemoglobin oxygen saturation caused by medetomidine, making them extremely low in many sheep. In addition, medetomidine also reduced blood haemoglobin concentration, which may potentiate the effects of low haemoglobin oxygen saturation. PaO_2 did not correlate with $PaCO_2$; e.g. at 5 min after medetomidine-midazolam injection the highest (6.2 kPa) and the lowest (4.8 kPa) $PaCO_2$ were detected in sheep that had extremely low PaO_2. This indicated that the marked hypoxaemia was not caused by hypoventilation. A more probable explanation for the hypoxaemia might have been pulmonary shunts. Marked hypoxaemia was the probable reason for the cardiac arrests in one sheep, as the PaO_2 detected in this sheep after medetomidine-midazolam injection varied between 3.7 and 4.2 kPa.

In conclusion, midazolam potentiates the sedative effect, but also the decrease in arterial O_2 tension and haemoglobin oxygen saturation in-

duced by medetomidine in sheep, causing a marked hypoxaemia. One sheep had to be resuscitated twice after the medetomidine-midazolam injection. The results indicate that this drug combination is unsafe for sheep.

References

Alibhai HIK, Clarke KW, Lee YH, Thompson J: Effects of atropine sulphate and medetomidine hydrochloride combinations on the cardio-pulmonary system in dogs and sheep. J. vet. Anaesth. 1993, *20,* 47.

Dueck R, Schroeder JP, Parker HR, Rathbun M, Smolen K: Carotid artery exteriorization for percutaneous catheterization in sheep and dogs. Amer. J. vet. Res. 1982, *43,* 898-901.

Hayashi K, Nishimura R, Yamaki A, Kim HY, Matsunaga S, Sasaki N, Takeuchi A: Comparison of sedative effects induced by medetomidine, medetomidine-midazolam and medetomidine-butorphanol in dogs. J. vet. Med. Sci. 1994, *56,* 951-956.

Hayashi K, Nishimura R, Yamaki A, Kim HY, Matsunaga S, Sasaki N, Takeuchi A: Cardiopulmonary effects of medetomidine, medetomidine-midazolam and medetomidine-butorphanol in dogs. J. vet. Med. Sci. 1995, *57,* 99-104.

Ilkiw JE, Suter C, McNeal D, Steffey EP: Behavioral effects of midazolam following intravenous and intramuscular administration in healthy awake cats. Vet. Surg. 1991, *20,* 157.

Kaneko JJ: Appendixes. In: (Ed) Kaneko JJ: Clinical Biochemistry of Domestic Animals, 4th edn. Academic Press Inc., San Diego, pp 877-901.

Kyles AE, Waterman AE, Livingstone A: Antinociceptive activity of midazolam in sheep. J. vet. Pharmacol. Therap. 1995, *18,* 54-60.

Laitinen OM: Clinical observations on medetomidine/ ketamine anaesthesia in sheep and its reversal by atipamezole. J. Ass. vet. Anaesth. 1990, *17,* 17-19.

Michaloudis DG, Kanakoudis FS, Xatzikraniotis A, Bischiniotis TS: The effects of midazolam followed by administration of either vecuronium or atracurium on the QT interval in humans. Eur. J. Anaesthesiol. 1995, *12,* 577-583.

Nishimura R, Kim HY, Matsunaga S, Hayashi K, Tamura H, Sasaki N, Takeuchi A: Sedative effect induced by medetomidine and midazolam in pigs. J. vet. Med. Sci. 1993a, *55,* 717-722.

Nishimura R, Kim HY, Matsunaga S, Hayashi K, Tamura H, Sasaki, Takeuchi A: Comparison of sedative and analgesic/anesthetic effect induced by medetomidine, acepromazine, azaperone, droperidol and midazolam in laboratory pigs. J. vet. Med. Sci. 1993b, *55,* 687-690.

Nishimura R, Kim HY, Matsunaga S, Hayashi K, Tamura H, Sasaki N, Takeuchi A: Cardiopulmonary effects of medetomidine, medetomidine-midazolam and medetomidine-midazolam-atipamezole in laboratory pigs. J. vet. Med. Sci. 1994, *56,* 359-363.

Salonen M, Onaivi ES, Maze M: Dexmedetomidine synergism with midazolam in the elevated plus-maze test in rats. Psychopharmacol. 1992, *108,* 229-234.

Tulamo R-M, Raekallio M, Ekblad A: Cardiovascular effects of medetomidine-ketamine anaesthesia in sheep, with and without 100% oxygen, and its reversal with atipamezole. J. vet. Anaesth. 1995, *22,* 9-14.

Sammanfattning

Sedering med medetomidin och midazolam hos får.

Sju får behandlades 3 gånger: med medetomidin (15 $\mu g\ kg^{-1}$), med midazolam (0.1 mg kg^{-1}) och med kombination av medetomidin och midazolam. Alla läkemedel gavs intravenöst. Hjärt- och andnigsfrekvens mättes. Arteriella blodprov togs, och PaO_2, $PaCO_2$, pH, koncentration av hemoglobin och dess syremättnad, och basöverskott bestämdes. Systoliskt och medelblodtryck mättes under sedering med kombinationen av medetomidin och midazolam.

Tiden som fåren låg ner var längre, när midazolam gavs tillsammans med medetomidin. Vid administrering av enbart midazolam blev några får sederade, medan de andra blev upphetsade. Hjärtfrekvensen sjönk både efter medetomidin och medetomidin-midazolam. Systoliska och medelblodtrycket sjönk efter medetomidin-midazolam. Ett får fick hjärtstillestånd efter medetomidin-midazolam och behövde återupplivning. PaO_2 och hemoglobinets syremättnad minskade och $PaCO_2$ ökade efter både medetomidin och medetomidin-midazolam, men artärblodets pH var inom riktvärdena efter alla behandlingar.

Resultaten i denna studie tyder på, att midazolam förstärker den lugnande verkan av medetomidin, men potentierar samtidigt sänkningen av PaO_2 och hemoglobinets syrehalt framkallade av medetomidin hos får.

(Received January 8, 1997; accepted December 8, 1997).

Reprints may be obtained from: M. Raekallio, Department of Clinical Sciences, Faculty of Veterinary Medicine, P.O. Box 57, FIN-000 14, University of Helsinki. E-mail: Marja.Raekallio@Helsinki.Fi, tel: +358 9 70849669, fax: +358 9 70849670.