Influence of romifidine and detomidine on the induction of anesthesia and recovery from total intravenous anesthesia in horses

De invloed van romifidine en detomidine op de inductie en recovery bij paarden in combinatie met totale intraveneuze anesthesie

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ABSTRACT

In the present study, the quality of the induction of and the recovery from anesthesia was compared in 146 horses undergoing total intravenous anesthesia with guaifenesin, ketamine and detomidine for computed tomography (CT), randomly assigned to receive either romifidine (n = 110) or detomidine (n = 36) during premedication. The induction of anesthesia was performed with a ketamine-midazolam combination. The anesthetic duration was short (mean +/- SD time: 23.5 +/- 8.8 minutes). No significant difference in induction score was observed. However, the recovery quality was significantly better in horses premedicated with romifidine.

SAMENVATTING

In de voorliggende studie werd de kwaliteit van de inductie en de recovery vergeleken bij 146 paarden na totale intraveneuze anesthesie met guaifenesine, ketamine en detomidine, ten behoeve van computertomografie (CT). Ze werden willekeurig ingedeeld, waarbij de ene groep romifidine (n=110) en de andere groep detomidine (n=36) als premedicatie kreeg. De anesthesie werd geïnduceerd met een combinatie van ketamine/midazolam. De gemiddelde anesthesieduur van de CT was kort (gemiddeld +/- SD: 23,5 +/- 8,8 minuten). Er bleek geen significant verschil te zijn voor de inductiescore. Wel bleken paarden gepremediceerd met romifidine een significant betere recoveryscore te hebben.

INTRODUCTION

Alpha-2 agonists are synthetic drugs that cause sedation, analgesia and myorelaxation due to their interaction with alpha-2 adrenoreceptors that are widely distributed throughout the body. Analgesia is thought to be the result of actions on the supraspinal and spinal sites in the central nervous system, while sedation is the effect of supraspinal stimulation of alpha-2 receptors in the locus coeruleus (Williams et al., 1985). As such, alpha-2 agonists are generally used in veterinary practice to tranquilize animals (i.e. pharmacologic restraint). This facilitates diagnostic examinations of minimally invasive and minor surgical procedures, and limits stress experienced by the patient (Nannarone et al., 2007). Furthermore, alpha-2 agonists are used for premedication prior to general anesthesia (Clarke and Gerring 1990; Taylor et al. 2001; Wojtasiak-Wypart et al., 2012), and are often a component of intravenous (IV) drug regimens for the maintenance of general anesthesia (Kerr et al., 2004; Rossetti et al., 2008; Wojtasiak-Wypart et al., 2012).

Total intravenous anesthesia (TIVA) is generally used for short field procedures. A study by Luna et al. (1996) is consistent with that of Taylor and Watkins (1992), both demonstrating that a combination of guaifenesin, ketamine and detomidine is a reliable alternative to halothane anesthesia. Specifically, Taylor et al. (1992, 1995) reported that maintenance of anesthesia with this combination for two hours produced a stable cardiorespiratory function and depression of the pituitary-adrenal activity during surgery in ponies and horses. Pharmacokinetic studies performed during TIVA using the original infusion rates described by Greene et al. (1986), indicated that guaifenesin concentrations increased, reaching dangerously high values after two hours of anesthesia (Taylor et al., 1995). A lower infusion rate of guaifenesin is more likely to facilitate a better recovery (Luna et al., 1996).

Recovery from general anesthesia in horses is a

Table 1. Comparison of the influence of romifidine and detomidine on the induction of anesthesia and recovery from total intravenous anesthesia in horses.

	Detomidine	Romifidine
Number of horses	36	110
Number of mares	13	49
Number of geldings	18	57
Number of stallions	4	5
Mean duration of Anesthesia (min)	23.5	23.6
Mean duration of recumbancy during recovery (min)	32.5	35
Mean number of attempts to stand	2.7	1.2
Number of horses receiving extra premedication	9	31
Mean induction score (1-5)	2.02	2.07
Median induction score (range)	2 (1-4)	2 (1-5)
Mean recovery score (1-5)	2.9	1.8
Median recovery score (range)	3 (1-5)	2 (1-4)

Table 2. Number of breeds.

Breed	Number
Dutch Warmblood	90
Dutch Riding horse	8
Quarter horse	8
Friesian	6
Oldenburger horse	4
Hanoverian	3
Appaloosa	2
Arabian	2
Bavarian Warmblood	2
Belgian Warmblood	2
Rheinlander	2
Tinker	2
Welsh pony	2
Westfaler	2
Andalusian horse	1
Fjord	1
Haflinger	1
Standardbred	1
Trakhener	1
Unknown	6
Total	146

critical and difficult period to manage and the risk of complications, including death, is higher than in other species (Johnston et al., 2002; Schauvliege and Gasthuys, 2012). Once the horse regains consciousness, it tries to stand and the first attempts may be unsuccessful, causing the horse to enter into a state of confusion. Both excitement and ataxia are often observed, which can typically lead to injury of the horse simply due to the large size and temperament of the animal that may have just undergone a surgical procedure (Matthews et al. 1992; Santos et al. 2003). Johnston et al. (2002) reported a death rate of 0.9%, based on data collected from more than 40,000 general anesthetics of "non-colic horses" (information obtained from 62 clinics), where fractures and myopathies were the cause of 32% of the postanesthetic deaths. To reduce the number of unnecessary postanesthetic deaths, several strategies can be employed to ensure a calmer recovery period, such as an optimal choice of anesthetic and analgesic protocols as well as tailored conditions for anesthetic maintenance and recovery (Matthews et al. 1992; Santos et al. 2003; Schauvliege et al. 2011; Marcilla et al. 2012).

The objective of the current study was to evaluate and compare the quality of induction and recovery in horses anesthetized with total intravenous anesthesia after premedication with two different alpha-2 adrenergic receptor agonists, romifidine (group R) (Sedivet®, Boehringer Ingelheim, Alkmaar, the Netherlands) and detomidine (group D) (Domosedan®, Pfizer Animal Health, Capelle aan de IJssel, the Netherlands).

MATERIALS AND METHODS

Patients

In total, this study included 146 horses (62 mares, 9 stallions and 75 geldings), ranging in age from 1 to 18 years old with an average weight of 561 ± 75 kg (Table 1). Roughly 75% of the horses were of a Warmblood type (Table 2).

All patients were examined by computed tomography (CT), mostly of the distal limb. The preanesthetic examination included general impression, body condition score (BCS: 1–3), appetite, weight, general clinical examination and auscultation of heart and lungs. Only American Society of Anaesthesiologists

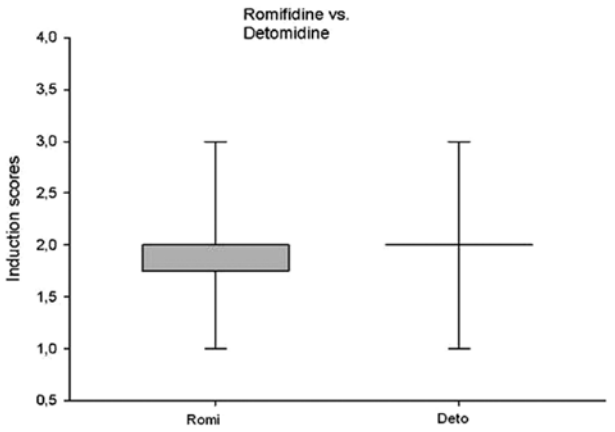

Figure 1. Comparison of the induction grade of detomidine versus romifidine.

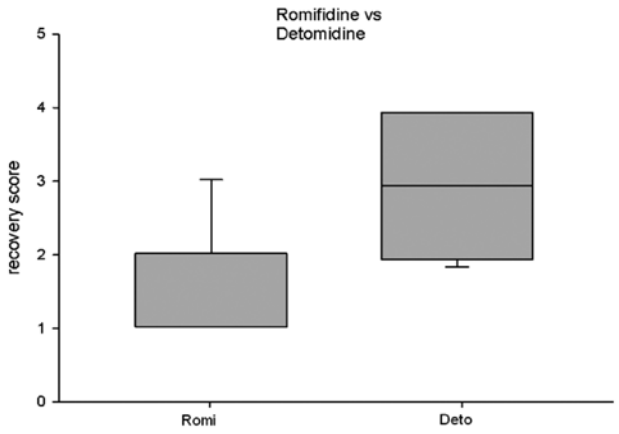

Figure 2. Comparison of the recovery grade of detomidine versus romifidine.

(ASA) class 1 (normal healthy patient) and two (patient with mild systemic disease; no functional limitation) patients were included in the study.

Experimental design

Horses were randomly assigned to group R (romifidine: 110 horses) or group D (detomidine: 36 horses) (Table 1). The corresponding drugs were administered intravenously according to the manufacturer's recommendations (romifidine at 80 mg/kg and detomidine at 10 mg/kg).

Five minutes after intravenous administration, an experienced anesthesiologist blinded to the protocol assessed the depth of sedation using previously described methods (Figueiredo et al., 2005) and, if necessary, a supplement of the same alpha-2 agonist was administered to achieve the desired depth of sedation (deep sedation, stage 3, defined as: markedly decreased frequency and velocity of movement, pronounced ear tip separation, markedly lower neck carriage, greatly reduced eye alertness, extreme lip separation, markedly increased base-wide stance, increased occurrence and severity of crossed legs, buckled knees, and/or fetlocks, and pronounced loss of postural tone).

A 12-gauge catheter was placed aseptically into the jugular vein. The induction of anesthesia was performed with a ketamine-midazolam combination (2 mg/kg ketamine (Nimatek®, Eurovet Animal Health, Bladel, the Netherlands) and 0.06 mg/kg midazolam (Dormicum®, Aesculaap, Boxtel, the Netherlands)) administered from one syringe immediately after preparation. Anesthesia was maintained with TIVA using a triple drip containing 500 ml 10% guaifenesin (Gujatal®, Eurovet Animal Health, Bladel, the Netherlands) to which 1000 mg ketamine and 10 mg detomidine were added, to obtain concentrations of 100mg/ml guaifenesin, 2mg/ml ketamine and 0.02mg/ml detomidine, with a constant rate infusion (CRI) of 1 ml/kg/h.

One veterinarian and one assistant, both blinded to the protocol, assisted the horses with head and tail ropes during the recovery from anesthesia, supporting the horse only when necessary.

Measured and calculated variables

The principal investigator in charge of data collection was blinded to the premedication protocol. Two independent observers blinded to the protocol evaluated the quality of induction and recovery from general anesthesia of each horse using predetermined simple descriptive scales (SDS), with scores ranging from 1 (good recovery) to 5 (poor recovery) (Tables 3 and 4).

Anesthetic duration was measured from the moment the horse was placed on the CT-table until the time that it was removed from the table. The time of recumbency and the time to release from head and tail ropes (i.e. horse is able to stand firmly) during assisted recovery were measured. The number of attempts needed to stand was also recorded.

Statistical analysis

The induction and recovery scores are presented as medians and ranges (Table 1). Continuous data (duration of recovery, etc.) are shown as mean ± s.d. The BCS data are summarized as numbers and percentages. Differences in induction and recovery scores between groups were compared using a Mann-Whitney U test. Statistical analysis was performed in SPSS version 15.0. Statistical significance was defined at $p < 0.05$.

RESULTS

The duration of anesthesia (Table 1) was short in all cases. The overall mean anesthetic time was 23.5 minutes, with a maximum of 50 minutes. For group R, the mean anesthetic time was 23.7 minutes (SD

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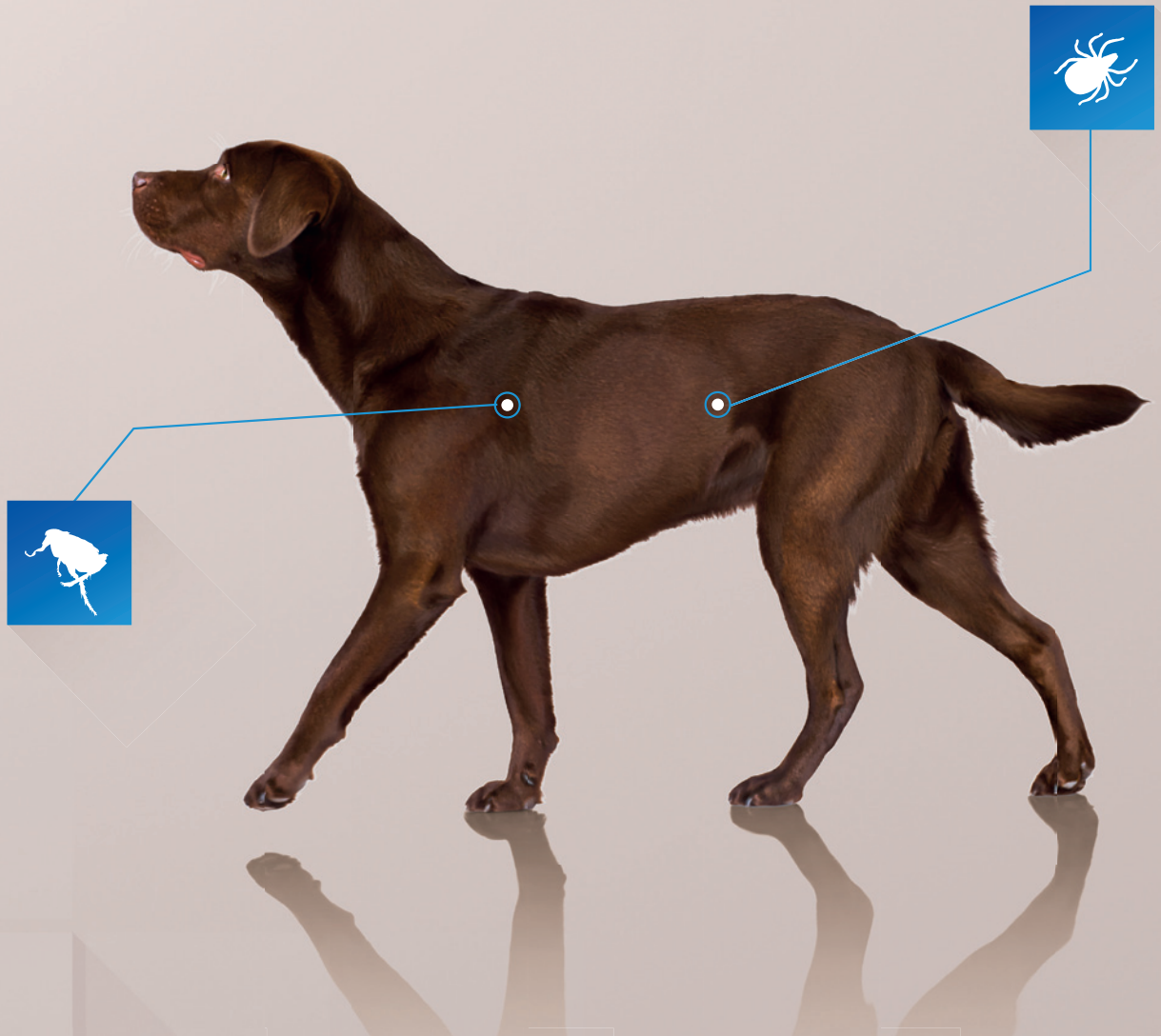

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de baten/risicobeoordeling van de behandelend dierenarts. Dosering en toedieningsweg: Orale toediening. Dosering: 2,7–6,9 mg/kg lichaamsgewicht, overeenkomend met 1 NEXGARD 11 mg kauwtablet voor 2-4 kg; 1 NEXGARD 28 mg kauwtablet voor >4-10 kg; 1 NEXGARD 68 mg voor >10-25 kg en 1 NEXGARD 136 mg kauwtablet voor >25-50 kg. Gebruik een geschikte combinatie van kauwtabletten van verschillende/dezelfde sterkte voor honden boven 50 kg lichaamsgewicht. De tabletten mogen niet worden gedeeld. Methode van toediening: De tabletten zijn kauwbaar en smakelijk. Indien niet direct geaccepteerd, kunnen ze worden toegediend met voedsel. Behandelschema: Maandelijkse intervallen gedurende het vlooien- en/of tekenseizoen, gebaseerd op lokale epidemiologische situaties. EU/2/13/159/001–012 (REG NL 112859-62). Uitsluitend op diergeneeskundig voorschrift verkrijgbaar diergeneesmiddel (UDA). Verdere informatie beschikbaar bij Merial Belgium NV, Leonardo Da Vincilaan 19, 1831 Diegem of Merial B.V., Kleermakerstraat 10, 1991 JL Velserbroek. fs220114. MattArt 16994_1/03/14

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Table 3. Scoring system used to grade induction.

Score	Characteristics
1	Very easy induction, with smooth relaxation of the hind before the front
2	Very easy induction, with smooth relaxation of the front before the hind
3	Anxiety during induction but no supplement necessary
4	Anxiety during induction; the horse requires ketamine supplement, but has an appropriate depth of anesthesia after induction
5	Difficult induction despite administration of a supplement

9.17 minutes), and for group D the mean anesthetic time was 24.3 minutes (SD 8.1 minutes); moreover, the mean total volumes of CRI were similar in both groups. The mean number of attempts to stand for all horses was 1.54; for group R, it was 1.19, and for group D, it was 2.71.

BCS was also similar in both groups. Six horses (4%) had BCS 1 (thin), 112 horses (76%) had BCS2 (normal) and 29 horses (20%) had BCS3 (fat).

Since the induction and recovery scores of the horses that were supplemented with additional alpha-2 agonists during premedication were not statistically different from those that were not supplemented, these groups were combined for subsequent analysis.

No significant differences were observed in induction score (Table 1) between group R and group D ($p = 0{,}749$) (Figure 1). Twenty-four percent of the horses in group R versus 20% in group D had an induction score of 3 or more.

Significant differences were observed in recovery score (Table 1) between group R and group D ($p < 0.001$) (Figure 2). In total, 13.5% of the horses in group R and 61% of the horses in group D had a recovery score of 3 or more.

DISCUSSION

In this study, the recovery quality was significantly better in the horses premedicated with romifidine than in the horses premedicated with detomidine, with no loss in the quality of induction.

The difference in recovery quality between the two drugs might be caused by their difference in duration of action. The half-life and duration of action are longer for romifidine (Wojtasiak-Wypart et al., 2012), than for detomidine (Salonen et al., 1989). Also other authors reported that sedation lasted longer when romfidine was used (Jochle and Hamm,1986; England et al., 1992). However, according to Rohrbach et al. (2009), romifidine (0.08mg/kg) and detomidine (0.02mg/kg) have similar sedative effects for approximately 90 minutes. In the present study, the same dose of romifidine was used; as for detomidine however, only 0.01mg/kg was administered. Taking this into consideration, the duration of action of detomidine should be shorter or less effective. As CT is a short procedure, the longest anesthetic duration time was 50 minutes, with a mean anesthetic time of 23.5 +/- 8.8 minutes. In all of the cases of this study, the sedative effect of romifidine should still have been present during recovery. According to Santos et al. (2003), the administration of alpha-2 adrenoceptor agonists during recovery from isoflurane anesthesia in horses prolong and improve the quality of recovery, showing less ataxia. Concluding the effect was greater during recovery for group R than for group D, this could explain calmer horses and a quieter and more effective recovery in group R.

Another explanation for the difference in recovery quality could be the degree of ataxia that is produced by both drugs. According to Hamm et al. (1995), the recommended dose of detomidine (10µg/kg) achieves a greater sedative effect, with more pronounced instability and ataxia, which could explain why the horses premedicated with detomidine were unable to stand as steadily during recovery as those, which were administered romifidine, and why they typically required more attempts to stand (mean number of attempts being 2.71 for group D versus 1.19 for group R). As in the present study, the depth of sedation (stage 3, where the symptoms of ataxia are one of the parameters) was similar for both groups, which was assessed by an experienced anesthesiologist blinded to the protocol, this is not expected to be a relevant explanation for the difference in recovery quality.

A third explanation may be found in the difference in selectivity for alpha-2-receptors. The pharmacological response to an agonist depends on the affinity of the agonist for the receptor, the efficacy of the agonist and the number of receptors available (Ahrens et al., 1996). The sedative effects of alpha-2 agonists are mainly mediated by the stimulation of alpha-2 receptors in the locus coeruleus, the pons and the lower brainstem (Williams et al., 1985; Scheinin and Schwinn, 1992). Stimulating alpha-1-receptors causes smooth muscle contraction, which might cause adverse side effects. These side effects are for example secretion from sweat glands, vasoconstriction in the skin, mucosa and abdominal viscera, but also vasoconstriction in the brain. The selectivity of the drugs for

Table 4. Scoring system used to grade recovery.

Score	Characteristics
1	Horse stands up without help from the assisted recovery system
2	Horse needs some help from the assisted recovery system to get up, but stands firmly
3	Horse needs help to get up and keeps stumbling after it got up
4	Horse needs help to get up and falls down after getting up
5	Horse cannot get up even with help from the assisted recovery system

alpha-2 and alpha-1 receptors (alpha-2/alpha-1-ratio) is different. Detomidine is less specific than romifidine. The alpha-2/alpha-1 selectivity binding ratio of detomidine is 260, whereas this value is 340 for romifidine (Virtanen, 1986; Cornick-Seahorn, 2000; Rohrbach et al., 2009). Concluding that romifidine is more specific, this might be responsible for its more pure sedative effect.

A last reason for the difference in recovery quality could be that the horses of group R were premedicated with romifidine and received detomidine during CRI, while the horses of group D only received detomidine. There might have been an interaction between romifidine and detomidine in group R, or the answer may be found in a different plasma concentration of detomidine. In a study by Taylor et al. (1995), the maintenance of anesthesia with detomidine, ketamine and guaifenesin during a period of two hours produced stable cardiorespiratory function and depression of pituitary-adrenal activity during surgery. However, whereas stable concentrations of guaifenesin and ketamine were achieved, stable concentrations of detomidine were not observed. Furthermore, there was a wide variability at each sampling time.

Future studies are required to assess the influence of the use of different alpha-2 agonists during the maintenance of general anesthesia with TIVA CRI. The authors of this study deliberately chose not to change the TIVA composition to limit experimental variables. Based on the results of this study, it may be interesting to assess the influence of the different alpha-2 agonists in TIVA CRI on the quality of recovery/anesthesia.

The recovery scoring system used in the current study is very clear and based on the level of assistance necessary during recovery. Recovery scoring systems used in other studies, e.g. in the study by Young and Taylor (1993) using grade 1-5 or the numerical scoring system described by Donaldson et al. (2000), do not take assisted recovery into account.

A limitation of the present study is the discordance in the number of horses premedicated with romifidine (n=110) and the number of horses premedicated with detomidine (n=36). Nevertheless, statistical evaluation showed obvious differences between romifidine- and detomidine premedicated horses.

CONCLUSION

In conclusion, the present study demonstrates that premedication with romifidine results in significantly better recoveries without any decreased quality of induction of general anesthesia than premedication with detomidine. Further studies are necessary to assess the possible reasons for the differences in recovery quality.

REFERENCES

Ahrens F.A., Dyer D., Hsu W.H., Riedesel D., Ware W.A. (1996). Drugs affecting peripheral neurohumoral transmission. In: *National Veterinary Medical Series: Pharmacology*. First edition, Lippincott William & Wilkins, Iowa, p 26.

Clarke K.W., Gerring E.L. (1990). Detomidine as a sedative and pre-medicant in the horse (1985-1990).In: *Proceedings of the Annual Convention of the American Association of Equine Practitioners 36*, 629-635.

Cornick-Seahorn J.L. (2000). Pharmacology and application of parenteral anaesthetic agents. In: *The practical Veterinarian Veterinary Anaesthesia*. First edition, Buttersworth-Heinemann, Waltham, Massachusetts, USA, p 45.

Donaldson L.L., Dunlop G.S., Holland M.S., Burton B.A. (2000). The recovery of horses from inhalant anaesthesia: a comparison of halothane and isoflurane. *Veterinary Surgery 29*, 92-101.

England G.C., Clarke K.W., Goossens L. (1992). A comparison of the sedative effects of three alpha 2-adrenoceptor agonists (romifidine, detomidine and xylazine) in the horse. *Journal of Veterinary Pharmacology and Therapeutics 15*, 194-201.

Figueiredo J.P., Muir W.W., Smith J., Wolfrom G.W. (2005) Sedative and analgesic effects of romifidine in horses. *International Journal of Applied Research in Veterinary Medicine 3(3),* 249-258.

Greene S.A., Thurmon J.C., Tranquilli W.J., Benson, G.J. (1986). Cardiopulmonary effects of continuous intravenous infusion of guaifenesin, ketamine and xylazine in ponies. *American Journal of Veterinary Research 47,* 2364-2367.

Hamm D., Turchi P., Jöchle W. (1995). Sedative and analgesic effects of detomidine and romifidine in horses. *The Veterinary Record 136*, 324-327.

Jochle W., Hamm, D. (1986). Sedation and analgesia with Domosedan (detomidine hydrochloride) in horses: dose response studies on efficacy and its duration. *Acta Veterinaria Scandinavia, Supplement 82*, 69-84.

Johnston G.M., Eastment J.K., Wood J.L.N., Taylor, P.M. (2002). The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Veterinary Anaesthesia and Analgesia 29*, 159-170.

Kerr C.L., McDonell W.N., Young, S.S. (2004). Cardiopulmonary effects of romifidine/ketamine or xylazine/ketamine when used for short duration anaesthesia in the horse. *Canadian Journal of Veterinary Research 68*, 274-282.

Luna S.P.L., Taylor P.M., Wheeler M.J. (1996). Cardiorespiratory, endocrine and metabolic changes in ponies undergoing intravenous or inhalation anaesthesia. *Journal of Veterinary Pharmacology and Therapeutics 19*, 251-258,

Marcilla M.G., Schauvliege S., Segaert S., Duchateau L., Gasthuys, F. (2012). Influence of a constant rate infusion of dexmedetomidine on cardiopulmonary function and recovery quality in isoflurane. *Veterinary Anaesthesia and Analgesia 39*, 49-58.

Matthews N.S., Miller S.M., Hartsfield S.M., Slater M.R. (1992). Comparison of recoveries from halothane versus isoflurane anaesthesia in horses. *Journal of the American Veterinary Medical Association 201*, 559-563.

Nannarone S., Gialletti R., Veschini I., Bufalari A., Moriconi F. (2007). The use of alpha-2 agonists in the equine practice: comparison between three molecules. *Veterinary Research Communications 31(Supplement 1)*, 309-312.

Rohrbach H., Korpivaara T., Schatzmann U. (2009). Comparison of the effects of the alpha-2 agonists detomidine, romifidine and xylazine on nociceptive withdrawal reflex and temporal summation in horses. *Veterinary Anaesthesia and Analgesia 36,* 384-395.

Rossetti R.B., Gaido Cortopassi S.R., Intelizano T., de Lima Machado T.S., Ferreira da Cruz R.S. (2008). Comparison of ketamine and S(+)-ketamine, with romifidine and diazepam, for total intravenous anaesthesia in horses. *Veterinary Anaesthesia and Analgesia 35,* 30-37.

Salonen J.S., Vaha-Vahe T., Vainio O., Vakkuri O. (1989). Single-dose pharmacokinetics of detomidine in the horse and cow. *Journal of Veterinary Pharmacology and Therapeutics 12,* 65-72.

Santos M., Fuente M., Garcia-Iturralde R., Herran R., Lopez-Sanroman J., Tendillo F.J. (2003). Effects of alpha-2 adrenoceptor agonists during recovery from isoflurane anaesthesia in horses. *Equine Veterinary Journal 35*, 170-175.

Schauvliege S., Gasthuys F. (2012) Dissociatieve anesthesia bij paarden in de praktijk. *Vlaams Diergeneeskundig Tijdschrift 81,* 229-236.

Schauvliege S., Marcilla M.G., Verryken K., Duchateau L., Devisscher L., Gasthuys F. (2011). Effects of a constant rate infusion of detomidine on cardiovascular function, isoflurane requirements and recovery quality in horses. *Veterinary Anaesthesia and Analgesia 38,* 544-554.

Scheinin M., Schwinn D.A. (1992). The locus coeruleus. Site of hypnotic actions of alpha 2-adrenoceptor agonists? *The Journal of Anaesthesiology 76,* 873-875.

Taylor P.M., Watkins S.B. (1992). Stress responses during total intravenous anaesthesia in ponies with detomidine-guaiphenesin-ketamine. *Veterinary Anaesthesia and Analgesia 19*, 13-17.

Taylor P.M, Luna S.P.L., Sear J.W., Wheeler M.J. (1995). Total intravenous anaesthesia in ponies using detomidine, ketamine and guaiphenesin: pharmacokinetics, cardiopulmonary and endocrine effects. *Research in Veterinary Science 59,* 17-23.

Taylor P.M., Bennett R.C., Brearley J.C., Luna S.P.L., Johnson C.B. (2001). Comparison of detomidine and romifidine as pre-medicants before ketamine and halothane anaesthesia in horses undergoing elective surgery. *American Journal of Veterinary Research 62,* 359-363.

Virtanen R. (1986). Antinociceptive activity and mechanism of action of detomidine. *Journal of Veterinary Pharmacology and Therapeutics 9,* 286-292.

Williams J.T., Henderson G., North R.A. (1985). Characterisation of alpha2-adrenoreceptors, which increase potassium conductance in rat locus coeruleus neurons. *Neuroscience 14*, 95-101.

Wojtasiak-Wypart M., Soma L.R., Rudy J.A., Uboh C.E., Boston R.C., Driessen B. (2012). Pharmacokinetic profile and pharmacodynamic effects of romifidine hydrochloride in the horse. *Journal of Veterinary Pharmacology and Therapeutics 35,* 478-488.

Young S.S., Taylor P.M. (1993). Factors including the outcome of equine anaesthesia: a review of 1,314 cases. *Equine Veterinary Journal 25,* 147-151.