Comparison of detomidine and romifidine as premedicants before ketamine and halothane anesthesia in horses undergoing elective surgery

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Objective—To compare detomidine hydrochloride and romifidine as premedicants in horses undergoing elective surgery.

Animals—100 client-owned horses.

Procedure—After administration of acepromazine (0.03 mg/kg, IV), 50 horses received detomidine hydrochloride (0.02 mg/kg of body weight, IV) and 50 received romifidine (0.1 mg/kg, IV) before induction and maintenance of anesthesia with ketamine hydrochloride (2 mg/kg) and halothane, respectively. Arterial blood pressure and blood gases, ECG, and heart and respiratory rates were recorded. Induction and recovery were timed and graded.

Results—Mean (± SD) duration of anesthesia for all horses was 104 ± 28 minutes. Significant differences in induction and recovery times or grades were not detected between groups. Mean arterial blood pressure (MABP) decreased in both groups 30 minutes after induction, compared with values at 10 minutes. From 40 to 70 minutes after induction, MABP was significantly higher in detomidine-treated horses, compared with romifidine-treated horses, although more romifidine-treated horses received dobutamine infusions. In all horses, mean respiratory rate ranged from 9 to 11 breaths/min, Pa_{O_2} from 200 to 300 mm Hg, Pa_{CO_2} from 59 to 67 mm Hg, arterial pH from 7.33 to 7.29, and heart rate from 30 to 33 beats/min, with no significant differences between groups.

Conclusions and Clinical Relevance—Detomidine and romifidine were both satisfactory premedicants. Romifidine led to more severe hypotension than detomidine, despite administration of dobutamine to more romifidine-treated horses. Both detomidine and romifidine are acceptable α_2-adrenoceptor agonists for use as premedicants before general anesthesia in horses; however, detomidine may be preferable when maintenance of blood pressure is particularly important. (*Am J Vet Res* 2001;62:359–363)

Alpha^2-adrenoceptor agonists have been used for sedation and premedication of horses for many years. In the United Kingdom, xylazine hydrochloride was first used more than 30 years ago[1]; detomidine hydrochloride was introduced in 1986[2] and romifidine in 1992.[3] All 3 drugs are α_2-adrenoceptor agonists and, as such, induce profound sedation, bradycardia, ataxia, and hypertension followed by mild hypotension.[2,4,5] Duration of action is most prolonged for romifidine and briefest for xylazine. Administration of romifidine causes less ataxia than either detomidine or xylazine,[3,6] and analgesia is least pronounced with romifidine.[6] Despite the considerable cardiovascular effects of α_2-adrenoceptor agonists, these agents are widely used for premedication before administration of nonvolatile and volatile anesthetics.[7-11] The profound sedation induced by α_2-adrenoceptor agonists leads to calm and smooth anesthetic inductions in horses. Moreover, use of α_2-adrenoceptor agonists as premedicants in horses prevents the subsequent development of ketamine-induced excitement and convulsions.[12] Xylazine and detomidine have been used prior to anesthesia for many years,[7-10] and more recently, romifidine has been used in the same way.[11]

The effects of xylazine, detomidine, and romifidine, particularly in regards to the cardiovascular system, are similar.[4,5] However, there have been few studies comparing the effects of the different α_2-adrenoceptor agonists in a controlled manner under clinical conditions. Hence, there is debate as to which drug is best for any particular procedure; the final choice may depend simply on personal preference. The purpose of the study reported here was to perform a prospective, blinded, randomized trial to compare detomidine and romifidine for premedication before anesthesia for elective surgery in horses.

Materials and Methods

Administration of α_2-adrenoceptor agonists—One hundred client-owned horses scheduled for elective surgery at the Animal Health Trust were studied. Acepromazine (0.03 mg/kg of body weight) and sodium penicillin (30 U/kg) were administered intravenously 30 minutes before a 14-gauge catheter was placed in a jugular vein. Using a list of random numbers, each horse was assigned to receive either 0.02 mg of detomidine[a]/kg (group D, n = 50) or 0.1 mg of romifidine[b]/kg (group R, 50) intravenously immediately after jugular catheterization. In each case, the anesthetist was unaware of the identity of the α_2-adrenoceptor agonist administered. Syringes containing detomidine or romifidine were prepared by a nurse and labeled with the horse's identification number only. The commercial detomidine solution was diluted with sterile nonpyrogenic water immediately before administration so that the volume was the same as an equivalent dose of romifidine.

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Induction and maintenance of anesthesia—Anesthesia was induced with ketamine hydrochloride (2 mg/kg, IV). Time from ketamine injection to horses reaching lateral recumbency was measured in seconds, and the quality of induction was scored from 5 (excellent; horse lowered itself gently into sternal then lateral recumbency) to 1 (dangerous; horse excited and difficult to control). The trachea was intubated immediately after horses reached lateral recumbency, and anesthesia was maintained with halothane in oxygen, using a large-animal breathing circuit[c] and an out-of-circle vaporizer.[d] Fresh gas flow was set at 8 to 10 L/min for approximately 15 minutes and was then reduced to 10 ml/kg/min. Halothane was supplied at a sufficient concentration to prevent movement in response to surgery. The vaporizer setting was recorded at 10-minute intervals. Horses were hobbled and hoisted onto a padded operating table within 5 minutes of induction, and a 20-gauge catheter was placed in the facial, transverse facial, or lateral metatarsal artery as soon as possible thereafter. Electrocardiograms were recorded from a sternal-withers electrode configuration.[e] Arterial blood pressure was measured directly via the arterial catheter, and arterial blood samples were obtained at 30-minute intervals for measurement of Pa_{O_2}, Pa_{CO_2}, and pH, using a blood gas analyzer.[f] End tidal carbon dioxide was measured from a catheter in the proximal end of the endotracheal tube, using infra-red analysis.[g] Heart rate was obtained from the ECG and respiratory rate from the capnograph.

All horses received either phenylbutazone (4 mg/kg) or flunixin meglumine (1 mg/kg) intravenously before surgery began and tetanus antitoxin (3,000 U) subcutaneously during surgery. Dobutamine was infused when required to maintain the **mean arterial blood pressure (MABP)** ≥ 70 mm Hg. Initial dobutamine infusion rate was 0.25 µg/kg/min; rate was increased in 0.1 to 0.2 µg/kg/min increments after approximately 3 to 5 minutes as necessary. No upper infusion rate was set, and 2 µg/kg/min was the maximum rate used. **Intermittent positive pressure ventilation (IPPV)** was used if Pa_{CO_2} exceeded 75 mm Hg. Ventilation sufficient to maintain Pa_{CO_2} < 75 mm Hg was supplied; however, no attempt was made to ventilate to normocapnia (40 mm Hg). Incremental doses of ketamine (0.1 to 0.2 mg/kg) or thiopental sodium (1 to 2 mg/kg) were administered as required to deepen anesthesia. Glycopyrrolate was administered when heart rate decreased to < 25 beats/min. Occasionally, gentamicin sulfate was administered before surgery, if necessitated by the procedure, and butorphanol (0.02 to 0.1 mg/kg) during surgery, if the procedure was considered likely to cause considerable postoperative pain.

Postsurgical monitoring—After surgery, each horse was moved on the hoist into a padded recovery box, extubated, and allowed to breathe room air. When recovery appeared violent, xylazine (0.1 to 0.2 mg/kg) was given intravenously to prevent injury. Recovery was observed, and the quality of recovery was scored from 5 (excellent; horse stands calmly and safely at the first attempt) to 1 (dangerous; numerous attempts to stand, excitement, ataxia, severe risk of or actual injury). Times from disconnection of the halothane supply until the horse first moved, reached sternal recumbency, and stood were recorded in minutes.

Statistical analyses—Data were reported as mean ± SD, unless stated otherwise, and were analyzed, using a commercially available software program.[h] Parametric data from the 2 groups were compared by use of ANOVA followed by a Fisher paired least squares difference test when a significant difference was detected. Within groups, changes with time were assessed by use of repeated measures ANOVA followed by a Dunnett modified *t*-test when a significant difference was detected. Nonparametric data from each group were compared by use of the Mann Whitney *U* test. Significance was set at $P < 0.05$.

Results

The majority (58/100; 58%) of horses were young Thoroughbreds undergoing arthroscopy, and there were no significant differences in breed, sex, age, body weight, position during surgery, or type of surgery between groups (**Tables 1 and 2**). In both groups, induction time (ie, time to recumbency) was approximately 80 seconds, and most horses had an induction grade of 4 or 5; there was no significant difference between groups in induction quality or time.

Mean arterial blood pressure decreased during

Table 1—Characteristics of horses that received acepromazine and detomidine (0.02 mg/kg of body weight, IV; n = 50) or romifidine (0.1 mg/kg, IV; 50) as premedicants prior to induction and maintenance of anesthesia with ketamine and halothane, respectively

Characteristic	Detomidine	Romifidine
Age* (y)	7 ± 4	17 ± 5
Body weight* (kg)	461 ± 155	498 ± 99
Breed or type†		
Thoroughbred	29 (58)	29 (58)
Warmblood/hunter	17 (33)	15 (30)
Pony/Arabian	3 (6)	5 (10)
Quarterhorse/cob	1 (3)	1 (2)
Sex†		
Intact male	11 (22)	10 (20)
Castrated male	21 (42)	25 (50)
Intact female	18 (36)	15 (30)

*Data reported as mean ± SD. †Data reported as No. (%).

Table 2—Characteristics of anesthesia and surgery in horses that received acepromazine and detomidine (n = 50) or romifidine (50) as premedicants prior to induction and maintenance of anesthesia with ketamine and halothane, respectively

Characteristic	Detomidine	Romifidine
Induction time* (s)	81 ± 35	75 ± 28
Induction quality†		
5-Excellent	22 (44)	30 (60)
4-Good	15 (30)	15 (30)
3-Moderate	11 (22)	4 (8)
2-Poor	1 (2)	1 (2)
1-Dangerous	1 (2)	0 (0)
Position during surgery†		
Dorsal recumbency	22 (44)	26 (58)
Right lateral recumbency	13 (26)	3 (16)
Left lateral recumbency	15 (30)	13 (26)
Type of procedure		
Arthroscopy	18 (36)	22 (44)
Orthopedic	22 (44)	20 (40)
Soft tissue	4 (8)	4 (8)
Ophthalmic	5 (10)	3 (6)
Radiography/radiotherapy	1 (2)	1 (2)
Duration of anesthesia* (min)	100 ± 42	104 ± 42
Recovery time* (min)		
To first movement	26 ± 14	25 ± 14
To sternal recumbency	30 ± 14	30 ± 21
To standing	44 ± 21	40 ± 21
Recovery quality†		
5-Excellent	19 (38)	14 (28)
4-Good	16 (32)	22 (44)
3-Moderate	10 (20)	11 (22)
2-Poor	6 (12)	3 (6)
1-Dangerous	0 (0)	0 (0)

See Table 1 for key.

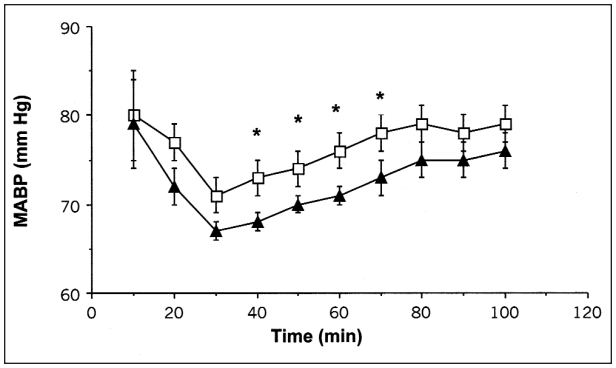

Figure 1—Mean (± SEM) mean arterial blood pressure in horses that received acepromazine and detomidine (0.02 mg/kg of body weight, IV; n = 50; □) or romifidine (0.1 mg/kg, IV; 50; ▲) as premedicants prior to induction and maintenance of anesthesia with ketamine and halothane, respectively. *Significant (P < 0.05) difference between groups.

anesthesia in both groups from 80 ± 35 mm Hg in group D and 77 ± 35 mm Hg in group R 10 minutes after induction to a nadir of 72 ± 14 and 67 ± 14 mm Hg, respectively, at 30 minutes (**Fig 1**). Blood pressure was significantly higher in group D than in group R from 40 to 70 minutes. Mean respiratory rate ranged from 10 to 11 breaths/min in group D and 9 to 11 breaths/min in group R. In both groups, mean Pa_{O_2} ranged between 200 and 300 mm Hg, mean Pa_{CO_2} between 59 and 67 mm Hg, and pH between 7.29 and 7.33. There were no significant differences between groups or changes with time in any respiratory or blood gas value. Number of horses that were ventilated did not significantly (P = 0.276) differ between groups (group D, 21 [42%]; group B, 15 [30%]). Exclusion of ventilated horses from analyses did not alter results for either respiratory rate or Pa_{CO_2}. Mean heart rate ranged from 31 to 33 beats/min in group D and 30 to 32 beats/min in group R. There were no significant differences in heart rate between groups or significant changes with time within groups, and no dysrhythmias were detected during anesthesia.

Vaporizer settings ranged from 4% during the first 10 to 20 minutes of anesthesia to between 1.5 and 2.5% for maintenance. There were no significant differences in vaporizer settings between groups at any time. Significantly (P = 0.009) fewer horses in group D (35 [70%]) required a dobutamine infusion to maintain MABP > 70 mm Hg, compared with group R (47 [94%]). Mean dobutamine infusion rate in group D was 0.38 ± 0.21 µg/kg/min over 80 ± 64 minutes; rate in group R was 0.42 ± 0.21 µg/kg/min over 77 ± 42 minutes. Rates did not vary significantly between groups. Dobutamine infusion was initiated between 20 and 30 minutes after induction in more than 80% of the 82 horses that required treatment. No horse received dobutamine before 10 minutes after induction. In 9 horses, dobutamine infusion was initiated more than 30 minutes after induction. Ten horses in group D and 12 in group R required 1 to 2 incremental doses of ketamine, and fewer than 4 horses in each group required thiopental sodium (1 to 2 mg/kg), glycopyrrolate (0.001 to 0.002 mg/kg), gentamicin (20 mg/kg), or butorphanol (0.05 to 0.1 mg/kg) during anesthesia or xylazine (0.1 mg/kg) during recovery. There were no significant differences between groups in use of any of these drugs.

No serious perianesthetic problems developed in any horse, and all recovered satisfactorily after anesthesia. In both groups, time to standing was approximately 40 minutes, and most horses (group D; 35 [70%]; group R, 36 [72%]) had a recovery quality grade of 4 or 5; there was no significant difference between groups in recovery quality or time to standing (Table 2).

Discussion

α_2-Adrenoceptor agonists are often used for premedication before induction of anesthesia with ketamine.[7-11] Use of these agents following acepromazine administration, particularly before maintenance of anesthesia with a volatile agent, is also common.[13,14] Although xylazine was the first α_2-adrenoceptor agonist to be used, detomidine became popular for premedication as soon as it was introduced in Europe.[9,10] Romifidine was introduced more recently but is now also commonly used for premedication.[11] The study reported here was designed to assess objectively the relative merits of 2 of these 3 agents when used as a premedicant.

Our data indicate that romifidine and detomidine had similar effects when used for premedication before general anesthesia in horses. The study was successful in comparing the 2 drugs under similar clinical conditions, as the 2 α_2-adrenoceptor agonists were the only variables compared in this prospective, randomized, blind study. Potentially confounding variables such as use of additional drugs, characteristics of the horses, and type of surgery were equally distributed between groups. Moreover, additional drugs were generally used in only a few horses in each group.

The exception to infrequent use of additional drugs was dobutamine. Administration of dobutamine was required to maintain MABP > 70 mm Hg in the majority of horses in both groups. A close association between hypotension during anesthesia and development of postoperative myopathy has been clearly demonstrated,[15,16] and it is now commonly accepted that postoperative myopathy is likely to develop as a result of inadequate muscle perfusion during anesthesia of hypotensive patients.[17] Dobutamine is frequently used to prevent or treat hypotension that usually develops in horses anesthetized with volatile agents,[18] and its use in this study reflects common clinical practice. Although dobutamine was required by more horses in group R, MABP in this group was significantly lower, compared with group D. Surgeries were performed at 1 clinic, where the practice was to use the minimum infusion rate of dobutamine that would maintain MABP > 70 mmHg. No upper limit for MABP was set; this was left to the anesthetist's judgment, and a MABP as high as 90 to 100 mm Hg would normally be tolerated. At the infusion rates used, treatment was usually adequate (MABP > 70 mm Hg) in group R but more than adequate (MABP considerably > 70 mm Hg) in group D. The experimental protocol did not set an upper limit for MABP. Thus, if the first infusion rate induced a MABP of 70 mm Hg, this rate was main-

tained, but if MABP increased to, for example, 80 mm Hg, this rate was also maintained. Hence, infusion rates were not significantly different between groups but MAPB was. Because the aim of the dobutamine infusion was to maintain MABP ≥ 70 mm Hg, dobutamine was infused to effect. The infusion rates used in this study were less than reported in previous studies.[19,20] Dobutamine may cause both tachy- and bradydysrhythmias at higher infusion rates, and our practice was to avoid development of dysrhythmias by starting dobutamine infusions cautiously with slow rates. In many cases, infusion rates as low as 0.25 µg/kg/min were sufficient to maintain MABP ≥ 70 mm Hg. Horses in group R appeared more resistant to the effects of dobutamine, and the anesthetist accepted lower MAPB for these horses for a prolonged period rather than increase the infusion rate too quickly or to a final rate > 2 µg/kg/min. Few horses (n = 5) developed MABP < 60 mm Hg, and in all cases, MABP in these horses had improved considerably within 20 minutes. Hence, although MABP in horses in group R achieved the desired value only after approximately 40 minutes, the clinical importance of low MABP in this group was probably limited; no horse developed myopathy. It is uncertain why horses in group R did not respond to dobutamine as well as those in group D. Had the experimental protocol included an upper limit on blood pressure, MABP may have been the same in both groups, and it is likely that infusion rates in group D would have been slower. Alternatively, the slow response to dobutamine in group R may have been a reflection of the prolonged depressant effects of romifidine, compared with detomidine.

In all other respects, data from group R and group D horses were similar. One of the major differences reported between romifidine and detomidine is the degree of ataxia that develops in sedated standing horses.[3,6] It may be supposed that this would affect induction and recovery quality. However, the agents induced similar results at both stages; even subjective assessment was unable to distinguish the 2 drugs. It is possible that the additional effects of acepromazine overrode any differences between the α_2-adrenoceptor agonists themselves.

More than one third of horses in both groups required IPPV to prevent $PaCO_2$ from increasing to > 75 mm Hg. Respiratory depression is a common feature of volatile anesthetic agents in horses, and our data are consistent with data from other studies.[10,21,22] The protocol dictated that IPPV should be used when $PaCO_2$ exceeded 75 mm Hg. Values less than this but greater than normal (40 mm Hg) were accepted, because results of 2 studies indicate that this degree of hypercapnia (40 mm Hg < $PaCO_2$ < 75 mm Hg) is not harmful to anesthetized horses and may actually benefit the cardiovascular system.[23,24] Removing data obtained from ventilated horses from the statistical analyses did not alter results, and the similarity between $PaCO_2$ in the ventilated and spontaneously breathing horses indicated that the experimental protocol was successful in maintaining $PaCO_2$ within the desired range whether horses were ventilated or breathing spontaneously. Because IPPV was required equally in both groups, these data are consistent with the view that detomidine and romifidine had similar effects on ventilation during anesthesia.

It is not surprising that administration of detomidine and romifidine induced broadly similar results. Both are α_2-adrenoceptor agonists and, as such, have been shown to have similar actions. Detomidine has fewer nonspecific effects on α_1-adrenoceptors than romifidine. Detomidine is considered to be 100 times more specific for α_2 adrenoceptors than xylazine, and specificity of romifidine is generally believed to fall between these values.[25] This difference in specificity may be expected to affect blood pressure, because α_1 stimulation increases peripheral resistance. However, in the present study, the converse occurred. Romifidine, the agent with greater α_1 effect, caused more hypotension. It is conceivable that the differential effects may relate to the individual effects of detomidine and romifidine at adrenoceptor subtypes or at the imidazole receptor, but our data do not allow more than speculation on such mechanisms.

On the basis of results from a previous study,[5] we believed that the doses of romifidine and detomidine used in the present study were equipotent. However, there is some suggestion that the effects induced by administration of 80 µg of romifidine/kg is equivalent to those induced by 20 µg of detomidine/kg.[5] Thus, the dose of romifidine we used may have been more potent than the dose of detomidine. This may also explain the effects of romifidine on blood pressure.

Results of the present study suggest that romifidine is an acceptable alternative to detomidine for premedication after acepromazine administration and prior to induction of anesthesia with ketamine and maintenance of anesthesia with halothane in horses. Although the differences between these 2 α_2-adrenoceptor agonists were limited, the decreased sensitivity to dobutamine infusion and slower resolution of hypotension after romifidine administration indicate that detomidine may be the better choice when prevention of hypotension is essential.

[a]Domosedan, Pfizer Ltd, Sandwich, UK.
[b]Sedivet, Boehringer Ingelheim Ltd, Bracknell, UK.
[c]Large animal anesthesia machine, JD Medical, Phoenix, Ariz.
[d]Mark III Fluotec, Cyprane, Keighley, UK.
[e]Kontron 108 system, Kontron Ltd, Watford, UK.
[f]Corning 680 blood gas analyzer, Corning Ltd, Halsted, UK.
[g]Datex capnograph, Datex, Helsinki, Finland.
[h]Statview SE+graphics, Abacus Concepts, Berkeley, Calif.

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