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Comparison of the sedative and cardiovascular effects of the combination of acepromazine-clonidine versus acepromazine-xylazine in horses

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Abstract

The aim of this study was to compare the sedative and cardiovascular effects of the combination of acepromazine-clonidine versus acepromazine-xylazine in horses. Four healthy cross-bred horses were included in the study. They were assigned to two treatments. In treatment I (T1), the animals received xylazine hydrochloride (1.00 mg kg^{-1}) in combination with acepromazine maleate (0.05 mg kg^{-1}) intravenously (IV). In treatment II (T2), the animals received intra-gastric administration of clonidine (0.002 mg kg^{-1}) followed by acepromazine (0.05 mg kg^{-1}; IV) after 60 min. Head height above the ground (HHAG) and echocardiographic indices were evaluated. In T1, recordings were made 5 min before and 5, 15, 30, 60, and 90 min after drug administration. In T2, recordings were made 5 min before clonidine, 55 min after clonidine administration, and then 5, 15, 30, 60, and 90 min after acepromazine injection. Analyses of the data showed there were not significant differences regarding HHAG and echocardiographic indices between two treatments. For sedation of healthy horses, it was concluded that intra-gastric administration of clonidine and IV administration of acepromazine showed similar sedative and cardiovascular effects compared to IV acepromazine-xylazine administration.

Introduction

The most commonly used drugs for standing sedation in horses are the alpha-2 agonists, which may be used alone or in combination with other drugs (e.g., opioids or phenothiazines). Acepromazine is a phenothiazine derivative commonly used in horses as a sedative during transportation and for clinical or surgical procedures.[1-4]

Xylazine has the potential for causing cardiovascular and respiratory depression, hyperglycemia with resultant diuresis, and abortions in late gestation.[5] It should not be used for animals with depressed cardiovascular function or urinary tract obstruction.[6]

Clonidine, 2-[(2,6-dichlorophenyl) imino]imidazolidine, is a potent drug used in the treatment of essential (i.e. primary) hypertension. The hypotensive effect of clonidine is due to stimulation of α-2-adrenergic receptors in the central nervous system.[7] Clonidine is classified as a class 3 performance-enhancing agent by the Association of Racing Commissioners International and thus, has the potential to influence the outcome of a race. During clinical testing of clonidine, it caused hypotension, sedation, and bradycardia in humans, which led to its introduction as an antihypertensive in human medicine.[8] For a number of years, clonidine has been marketed under several brand names for human use as a centrally acting alpha-2 agonist to decrease blood pressure.[9] Other centrally mediated effects of clonidine include sedation,[10,11] and analgesia.[7,12] Clonidine has also been reported to bear the potential to produce sedative or tranquilizing effects in horses.[13]

The aim of this study was comparison of sedative and cardiovascular effects of combination of acepromazine-clonidine versus acepromazine-xylazine in horse. Head height above the ground (HHAG) and echocardiographic indices were evaluated.

Materials and Methods

Procedures. Four cross-bred healthy horses (two males and two females weighing 385 - 450 kg, and 8 - 10

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years old) were included in this study. In this crossover clinical trial, animals were assigned to two treatment protocols with a washout period in between (see below) and because of small sample size, each protocol was repeated twice. In other words, for each treatment protocol eight data in each time point were obtained. Hence, for each treatment protocol eight horses were examined. All horses underwent clinical, hematological and parasitological examinations and were considered normal. Horses were together placed in stocks during the study period. The horses had free access to hay and water. The solid fasting period was 12 hr. Experimental protocols were performed for each horse on fixed days and periods (morning) and a 3-week washout period was followed between the experiments. For jugular injection of treatments, the region of the neck was clipped. For echocardiography, the region between 3rd and 5th inter-costal spaces was clipped, washed with surgical spirit and covered with acoustic coupling gel. The study was carried out in two treatment settings. In treatment I (T1), the animals received intravenous (IV) cocktail of 1.00 mg kg^{-1} xylazine (Alfasan, Woerden, The Netherlands) and 0.05 mg kg^{-1} acepromazine (Alfasan) in one syringe and volumes were equalized using normal saline. In treatment II (T2), the animals received intra-gastric administration of 0.002 mg kg^{-1} clonidine (Toliddaru, Tehran, Iran) followed by IV injection of 0.05 mg kg^{-1} acepromazine after 60 min. The tablets of clonidine were completely dissolved in 100 mL of warm water and administered as slurry via a nasogastric tube, followed by approximately 1,000 mL of warm water to rinse any remaining medication from the tube into the stomach. The pharmaceutical product of clonidine for IV injection was not available; therefore, the intra-gastric administration was used based on a method described by Mullen *et al*.[14] Head height above the ground and echocardiographic indices were recorded as follow. In T1, the parameters were evaluated 5 min before and 5, 15, 30, 60, and 90 min after the administrations. In T2, the parameters were evaluated 5 min before and 55 min after clonidine administration and then 5, 15, 30, 60, and 90 min after acepromazine injection were recorded. The time points were based on a modified protocol described by others.[13] The present study was carried out based on standard animal experimentation protocol of the Veterinary Ethics Committee of Urmia University, Urmia, Iran, and approved under ethical code of IR-UU-AEC-3/14.

Assessment of the HHAG. Ringer *et al*. adopted the HHAG as a marker of sedation depth. In brief, the HHAG is defined as a position of the nose in relation to a scale marked on the wall. The scale is individual to each horse and 100% indicates the normal head position (± 10.00%) of the particular horse while completely awake. The HHAG ≤ 50.00% indicates sufficient sedation. In this study, a modified method of Ringer *et al*. was adopted and the sedation depth was assessed measuring the degree of head drop following drugs administration.[15] Floor to chin height was determined in all times in both treatments and recorded.

Echocardiography. Echocardiographic images were acquired with an ultrasound device (Q9Vet; Chison Medical Technologies Co., Wuxi, China) with a phase array transducer (2.50 MHz). Region between 4th and 5th inter-costal spaces was used for echocardiography. The lack of cardiac anomaly was approved by right parasternal long and short axes echocardiography before initiation of treatment protocol. The M-mode echocardiography via right parasternal short axis view at the level of chordae tendinea was used to record following parameters by in-built software: Left ventricular internal diameter at end diastole (LVIDd), left ventricular internal diameter at end systole (LVIDs), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and fractional shortening (FS). A ventricular short axis view at the level of chordae tendinae was used to record M-mode images. The LVIDd was measured using the beginning of the QRS as the reference point, and LVIDs was measured at the maximum upswing of the left ventricular free wall.[15] The FS was determined by the following equation:

$$FS\ (\%) = (LVIDd - LVIDs) / LVIDd \times 100.$$

Statistical analysis. Data are presented as mean ± standard deviation. Statistical analysis was done with SPSS Statistic (version 22.0; IBM Corp., Armonk, USA). The Shapiro-Wilk test was used to check normal distribution. For comparison between groups, independent samples *t*-test and for inside group comparison, paired samples *t*-test was used. Qualitative data between groups were compared with chi-square and Kruskal-Wallis tests. Statistical differences with $p < 0.05$ were considered significant.

Results

Head height above ground. The results of HHAG for determining the degree of sedation are shown in Table 1. In T1, there was a decreasing trend until 5 min after acepromazine-xylazine administration, followed by an increasing trend. In T2, there was a decreasing trend until 15 min after drug administration, followed by an increasing trend. Overall, the lowest head height in T1 was observed at 5 min after drug administration; while, in T2 it was observed at 15 min after drug administration. Statistical analysis revealed a significant difference inside each group at 5, 15, 30, and 60 min after drug administration ($p < 0.05$).

Echocardiographic indices. Results of echocardiographic indices including LVIDd, LVIDs, SV, EDV, ESV, EF and FS are shown in Table 2.

Table 1. Head height above ground (%) at different time points in animals of two treatment groups.

Treatments	Time (min)					
	–5	5	15	30	60	90
T1	100 [a]	31.66 ± 3.89 [ab]	43.75 ± 2.26 [abc]	54.58 ± 3.96 [abcd]	85.00 ± 3.69 [abcde]	100 [a]
T 2	100	37.50 ± 3.98	34.58 ± 2.57	45.00 ± 3.01	77.91 ± 4.98	100

[abcde] Different superscripts in each row indicate significant differences among time points ($p < 0.05$).

Table 2. Echocardiographic indices at different time points in animals of two treatment groups.

Indices	Treatments	Time (min)					
		–5	5	15	30	60	90
LVIDd (cm)	**T1**	11.31 ± 1.00	8.63 ± 1.01	8.08 ± 0.98	10.57 ± 0.95	11.13 ± 0.95	11.51 ± 0.93
	T2	11.66 ± 0.54	10.15 ± 0.58	9.62 ± 0.58	10.23 ± 0.55	10.79 ± 0.56	11.05 ± 0.58
LVIDs (cm)	**T1**	8.58 ± 0.56	7.33 ± 0.55	6.92 ± 0.55	7.23 ± 0.42	7.52 ± 0.44	8.18 ± 0.44
	T2	8.75 ± 0.21	8.58 ± 0.21	8.26 ± 0.21	8.32 ± 0.41	8.54 ± 0.42	8.91 ± 0.49
EDV (mL)	**T1**	740.73 ± 138.72	523.12 ± 129.02	430.27 ± 132.29	481.26 ± 130.82	535.24 ± 131.06	630.59 ± 131.87
	T2	778.82 ± 87.26	600.18 ± 186.71	536.26 ± 84.92	580.42 ± 85.65	627.09 ± 82.59	774.87 ± 82.85
ESV (mL)	**T1**	413.81 ± 56.83	199.93 ± 54.18	110.66 ± 31.06	155.45 ± 31.34	214.39 ± 36.21	299.96 ± 32.86
	T2	432.36 ± 26.64	288.36 ± 30.57	221.90 ± 31.77	270.85 ± 32.95	289.35 ± 47.51	397.40 ± 104.16
SV (mL)	**T1**	326.92 ± 101.25	323.19 ± 84.15	319.61 ± 110.23	325.8 ± 109.66	320.85 ± 104.93	330.63 ± 107.76
	T2	346.45 ± 72.82	327.29 ± 75.42	314.36 ± 73.06	309.56 ± 74.85	337.73 ± 69.77	377.46 ± 109.51
EF (%)	**T1**	43.18 ± 8.01	61.74 ± 5.18	73.07 ± 7.61	66.11 ± 8.86	58.47 ± 8.71	51.00 ± 8.84
	T2	44.05 ± 4.87	52.61 ± 5.41	58.10 ± 5.78	54.42 ± 7.15	53.6 ± 6.43	48.61 ± 12.69
FS (%)	**T1**	23.88 ± 4.17	14.59 ± 6.31	13.84 ± 7.12	31.33 ± 3.44	32.23 ± 3.23	28.72 ± 2.92
	T2	24.89 ± 2.76	15.37 ± 3.99	13.89 ± 4.51	18.61 ± 3.04	20.74 ± 3.06	23.37 ± 2.96

LVIDd: Left ventricular internal diameter at end diastole; LVIDs: Left ventricular internal diameter at end systole; EDV: End-diastolic volume; ESV: End-systolic volume; SV: Stroke volume; EF: Ejection fraction; FS: Fractional shortening; T1: Treatment 1; T2: Treatment 2. There were no significant differences between two treatment protocols ($p > 0.05$).

Left ventricular internal diameter at end diastole findings. The results of LVIDd in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration, followed by an increasing trend. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

Left ventricular internal diameter at end systole findings. The results of LVIDs in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration, followed by an increasing trend. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

End-diastolic volume findings. The results of EDV in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration, followed by an increasing trend. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

End-systolic volume findings. The results of ESV in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration, followed by an increasing trend. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

Stroke volume findings. The results of SV in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration, followed by an increasing trend until 30 min after drug administration. From 30 to 60 min after drug administration, there was a decreasing trend followed by an increasing trend; but these changes were not noticeable. In T2, there was a decreasing trend until 30 min after drug administration, followed by an increasing trend which was also not noticeable. Based on the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

Ejection fraction findings. The results of EF in T1 and T2 showed that there was an increasing trend until 15 min after drug administration, followed by a decreasing trend. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

Fractional shortening findings. The results of FS in T1 and T2 showed that there was a decreasing trend until 15 min after drug administration. According to the statistical analysis, there were not significant differences between the two treatments during the time points ($p > 0.05$).

Discussion

The HHAG is a marker of sedation depth. It is defined as a position of the chin in relation to a scale marked on the wall. The scale is individual to each horse and 100% indicates the normal head position (± 10.00%) of the particular horse while completely awake. Reductions of the HHAG by 50.00% or more represent a sufficiently sedated animal.[16] In our study, mean values of HHAG were not significantly different

between two treatment protocols indicating that in both treatment protocols similar sedation depth was achieved within different time points.

Clonidine has been marketed for human use for a number of years as a centrally acting alpha-2 agonist to decrease blood pressure.[9] Other centrally mediated effects of clonidine include sedation[10,11] and analgesia,[7,12] and clonidine has the potential to produce sedative or tranquilizing effects as well as analgesia in horses.[13]

Based on Dirikolu *et al*., the rationale for administering alpha-2 agonists is that most horses experience pulmonary hypertension during running, leading to exercise-induced pulmonary hemorrhage, a considerable problem in horse-racing industry. Known as an anti-hypertensive in human medicine, clonidine could reduce pulmonary arterial blood pressure in racing horses and thus, potentially reduce the incidence or severity of exercise-induced pulmonary hemorrhage. On the other hand, as an alpha-2 agonist agent, clonidine may also have the ability to tranquilize or sedate horses and may also have some bronchodilator activity. Clonidine is currently classified as an Association of Racing Commissioners International class 3 agent.[12]

Dirikolu *et al.* showed that IV injection of clonidine at a dose of 0.025 mg kg^{-1} produced rapid, profound sedation as evidenced by relaxation of the lower lip, drooping of eyelids, and extreme head drop. As suggested by the rapidity of the head drop, the horses were clinically sedated within min of clonidine administration. The maximum sedative effect of clonidine was observed within 15 to 20 min after IV injection and persisted for 2.5 to 3 hr after injection.[12] In a study, Menzies-Gow administered acepromazine at a dose of 0.03 mg kg^{-1} to eight healthy horses intravenously and showed an increase in aortic and pulmonic diameters at the end of systole. The inter-ventricular septal width was also increased, both at the end of systole and diastole after acepromazine administration. In addition, there was a significant decrease in the LVIDd. Sedation did not affect the remaining cardiac dimensions, neither any indices of cardiac function, nor the occurrence and severity of valvular regurgitation, being concluded that diminishing in LVIDd might have been due to the hypotension induced by acepromazine.[17,18] Buhl *et al*. observed no effect of 0.10 mg kg^{-1} acepromazine administration on LVIDs and LVIDd.[18] There was no change in blood flow across valves in published studies.[14,18,19] One study reported that detomidine and romifidine increased the frequency of valvular insufficiency; whilst, acepromazine decreased the occurrence of regurgitation.[19] The dose of acepromazine in the study of Buhl *et al*. was 0.10 mg kg^{-1}; while, it was 0.03 mg kg^{-1} in the study of Menzies-Gow.[17,18] Dezfouli *et al*. used 0.01 mg kg^{-1} acepromazine only,[13] and as all of these three studies started the echocardiography 10 min after administration of acepromazine, the differences between results of these studies could be due to the differences in doses. Vasodilators cause dilation in peripheral arteries resulting in an increase in blood flow velocity and turbulence; this appears to explain the findings of Nogueira *et al*. for the combination of acepromazine and buprenorphine in dogs.[19] They used duplex Doppler to evaluate blood flow. Femoral artery flow velocity increased after administration of the drugs; but, flow volume was unaltered. In pigs, injection of vasoactive drugs caused peripheral vascular dilation and turbulent blood flow. It was found that the increase in blood flow seen in peripheral arteries after administration of acepromazine was the result of vasodilation and flow turbulence and not of cardiac origin.[20,21]

In a study in eight horses, administration of detomidine and romifidine caused an increase in the frequency of valvular regurgitation; whilst, acepromazine administration resulted in a decrease in the occurrence of regurgitation.[19] In study of Dezfouli *et al*. only a single horse developed aortic regurgitation (< 1.00 cm) after xylazine administration and acepromazine did not cause any regurgitation. It seems that acepromazine caused less regurgitation in comparison with other sedatives.[13]

Xylazine decreases the heart rate,[22] increases incidence of cardiac arrhythmia [23] and raises blood pressure.[24] In study of Dezfouli *et al.*, peripheral vascular resistance increased minimally after xylazine administration. Also, it was shown that xylazine had less cardiovascular and cardiac depressive effects than detomidine or medetomidine.[25] In another study, xylazine (1.00 mg kg^{-1}; IV) administration resulted in no statistically significant change in cardiac indices such as FS and EF.[26] The changes in blood pressure are the result of changes in peripheral resistance rather than changes in cardiac output.[26]

Patteson *et al.* showed that detomidine administration resulted in a significant increase in LVIDs, diameter of aorta at the level of the sinus of Valsalva and pre-ejection period. The LVFWs, IVSs, FS and heart rate all decreased significantly. They ascribed the reduction in cardiac performance to a decrease in myocardial contractility or an increase in after-load and also suggested that pre-load was not substantially altered by detomidine, despite a marked reduction in heart rate.[26] In another study, detomidine increased LVID, LVIDs and aortic dimensions and decreased IVSd and FS.[27,28]

In the study of Dezfouli *et al.*, LVIDs was significantly increased after xylazine and acepromazine administration.[13] An explanation for this was that there was an increase in pulmonary and aortic artery resistance as has been described for medetomidine.[29] This increase in pulmonary and aortic resistances would in turn increase right ventricle after-load and therefore RVIDs. This reflects the study of Yamashita *et al.*, finding that xylazine increased peripheral vascular resistance.[24] In our study, decreasing in LVIDd as a result of xylazine administration is a consequence of the vasoconstrictive effect of xylazine,

causing an increase in vascular resistance and subsequently, a reduction in pre-load. Buhl *et al*. reported a decrease in IVSs and FS after detomidine and romifidine administration and explained that this decline was a result of reduction in systolic left ventricular performance.[18] The IVSd was increased in our study, which may be the result of decreased pre-load and more bulging of the septum into the ventricle.[14] Indeed, changes in IVSd have an inverse relationship to LVIDd, as a reduction in LVIDd can result in an increase in IVSd as a result of decreased pressure on the septum and vice versa. In the study of Dezfouli *et al.*, FS was unchanged between groups, demonstrating no change in cardiac performance or contractility after xylazine or acepromazine administration.[13] In the present study, no change in cardiac performance or contractility following two treatments was observed.

In the present study, echocardiographic indices in T2 protocol were remained insignificant with T1 protocol, suggesting similar cardiovascular effect of clonidine compared to xylazine in combination with acepromazine.

Limitation of the present study was the small sample size. Actually, the small sample size of the present study is sufficient for an experimental study; however, may not be large enough to reflect field conditions. We used a low dose in T1 and T2 with minimal effects on echocardiographic measurements with the aim of inducing a light sedation to calm the horses and improve their restraint that could be considered as another limitation of our study. It should be noted that physiological tension and struggling action in the horse will change hemodynamics through increasing the heart rate and blood velocity as a result of sympathetic activation, which could alter echocardiographic indices within examination. It was concluded that intra-gastric administration of clonidine and IV administration of acepromazine showed similar sedative and cardiovascular effects compared to acepromazine-xylazine IV administration.

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Conflict of interest

There is no conflict of interest to declare.

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