Detomidine and xylazine, at different doses, in donkeys (*Equus asinus*)

Detomidina e xilazina, em diferentes doses, em asininos (*Equus asinus*)

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Abstract

The effects of detomidine and xylazine in donkeys were compared. Six animals were randomly assigned to six experimental groups: xylazine 10% at 0.8 mg/kg (xylazine group 0.8 – GX0.8), 1.0 mg/kg (GX1.0), and 1.2 mg/kg (GX1.2); and detomidine 1% at 20 µg/kg (Detomidine group 20 – GD20), 40 µg/kg (GD40), and 60 µg/kg (GD60), intravenously. Heart rate (HR) and respiratory rate (RR), rectal temperature (RT), mean arterial pressure (MAP), blood glucose, sedation, analgesia, ataxia, arrhythmias, and micción frequency were measured. Duration of sedation was greater in the groups in which detomidine was administered, lasting on average 140 minutes in GD60 and 47 minutes in GX1.2. Analgesia lasted 30 minutes in GD60 and only 10 minutes in the other groups in which detomidine and xylazine were used. There was a decrease in HR in GD20 and GD40 and atrioventricular block. There was a decrease in RT in GX1.2, GD20, GD40, and GD60. RR decreased in all groups. MAP increased in GD20, GD40 and GD60, five, 20, 30, and 10 minutes after administration of detomidine, respectively. Hyperglycemia occurred for 120 minutes in all animals receiving detomidine. Micción frequency was higher in GD60 (2.2 ± 0.8) than in GX0.8 (0.8 ± 0.4). In donkeys, detomidine and xylazine produce short-term analgesia and discreet cardiorespiratory changes and are safe and effective in the doses used.

Keywords: alpha-2 adrenergic agonist, analgesia, equine, sedation.

Resumo

Compararam-se os efeitos da detomidina e da xilazina em asininos. Foram utilizados, aleatoriamente, seis animais, os quais participaram de seis grupos experimentais: xilazina 10% 0.8 mg/kg (Grupo xilazina 0.8 - GX0.8), 1.0 mg/kg (GX1.0) e 1.2 mg/kg (GX1.2), e detomidina 1% 20 µg/kg (Grupo detomidina 20 - GD20), 40 µg/kg (GD40) e 60 µg/kg (GD60), administrados por via intravenosa. Foram monitorados: frequências cardíaca (FC) e respiratória (FR), temperatura retal (TR), pressão arterial média (PAM), glicemia, sedação, analgesia, ataxia, arritmias e micção. Duração da sedação foi maior nos grupos nos quais foi administrada detomidina, durando, em média, 140 minutos no GD60 e 47 minutos no GX1.2. Analgesia durou 30 minutos no GD60 e apenas 10 minutos nos demais grupos em que se utilizou a detomidina e nos grupos da xilazina. Ocorreu redução da FC no GD20 e no GD40 e bloqueio atrioventricular. Ocorreu redução na TR em GX1.2, GD20, GD40 e GD60. A FR diminuiu em todos os grupos. A PAM aumentou no GD20, GD40 e GD60 cinco, 20, 30 e 10 minutos após a administração da detomidina, respectivamente. Houve hiperiglicemia por 120 minutos em todos os animais que receberam detomidina. A frequência
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Introduction

Asinines have their own pharmacological characteristics that differentiate them from equines. Extrapolation of doses for drugs used in equines is common, which may cause inadequate sedation in donkeys undergoing clinical, diagnostic, or surgical procedures, due to these animals’ intolerance of audible, tactile, or nociceptive stimuli (Lizarraga et al., 2004; Grosenbaugh et al., 2011).

Sedation in donkeys is mainly obtained using alpha-2 adrenergic agonists. Associations with other drugs are commonly used in equines and aim to exacerbate sedative effects (Yamashita et al., 2000). The sedation produced by alpha-2 agonists results in lower head carriage, decreased consciousness, palpebral and labial ptosis, and ataxia. Evaluation of sedation in equines has been thoroughly studied (Ringer et al., 2012b; Ringer et al., 2013). However, in asinines, this evaluation is difficult because scoring systems for this species have not yet been validated.

The cardiorespiratory effects of alpha-2 agonists are dose-dependent and include bradycardia, atrioventricular block, and increased pulmonary and systemic vascular resistance (Ringer et al., 2012a).

In asinines, intravenous xylazine at a dose of 0.5 to 1.1 mg/kg produces sedative and mechanical antinociceptive effects (Lizarraga & Beths, 2012; Lizarraga & Janovyak, 2013; Lizarraga & Castillo-Alcala, 2015).

Detomidine is a more recent and more potent agonist than xylazine. Mostafa et al. (1995) evaluated the sedative effects of detomidine in asinines given various intravenous doses, and observed adequate sedation at doses of 5 and 10 µg/kg, and more intense sedation and analgesia with doses above 20 µg/kg.

Extrapolating pharmacological information obtained from the equine species to asinines does not take into consideration the morphophysiological and behavioral differences between horses and donkeys. Therefore, the objective of this research was to study the effects of various doses of xylazine and detomidine on some physiological parameters, as well as the sedation and analgesia produced in asinines. It is believed that the sedation caused by both drugs are co-dependent in these animals, as observed in other species.

Material and methods

Six adult, mixed-breed, healthy male donkeys, with a mean age of 6.5 ± 3 years, and weighing 118 ± 22 kg, belonging to breeders in the city of Patos, Paraíba, Brazil, were included. The study was approved by the Ethics and Research Committee of the institution where the study took place (Protocol CEP 13/2013). The animals were grouped and placed in a collective paddock measuring 20 X 22.5 m (total area of 450 m², or 75 m²/asinine), and were fed Tifton hay, water ad libitum, and commercial ration for equines at a quantity of 1% of live weight/day. An adaptation period of 15 days was instituted prior to the start of the experiment. During this period, each animal was led to the site of the study, where they remained within a structure for physical restraint (standing stock) for equids for approximately two hours. They were subjected to this routine several times until accustomed to it, and were able to enter and exit the standing stock calmly and without reluctance.

Each animal randomly participated in all the following experimental groups, with a seven day interval between treatments: xylazine 10%¹ at a dose of 0.8 mg/kg (Group xylazine 0.8 - GX0.8), 1.0 mg/kg (GX1.0), and 1.2 mg/kg (GX1.2); and detomidine 1%² at a dose of 20 µg/kg (Group detomidine 20 – GD20), 40 µg/kg (GD40), and 60 µg/kg (GD60). Both sedatives were administered intravenously, via puncture of the left external jugular vein.

¹ Sedazine 10% (Fort Dodge Saúde Animal Ltda., Brazil).
² Dormium V 1% (União Química Farmacêutica Nacional S/A, Brazil).
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After being fasted for 12 hours (solids), each animal was weighed and taken to the standing stock in the study room. Initially, basal values for the evaluated parameters were obtained, and the degree of sedation and ataxia the animal might have prior to administration of any drugs was also evaluated. After administration of the sedative, each animal was left on its own inside the standing stock until the end of the experimental period, after which they were taken back to their corral. The animal was removed from the stock only to evaluate the degree of ataxia caused by the sedatives.

To evaluate the degree of sedation, the following were measured: latency period (time between the end of the administration of the drug and start of sedation, characterized by labial and palpebral ptosis, and lowering of the head); intensity of the sedation (measured by the distance of the head to the ground, in centimeters, from the inferior lip to the ground, using a scale ruler with 10 cm marks, fixed on the lateral side of the standing stock); sedation phase (from the start of signs of sedation - labial and palpebral ptosis, lowering of the head and ataxia - until the animal no longer shows signs of sedation); and degree of ataxia after removing the animal from the stock and encouraging him to walk, monitored by the following grading scale: 0 - no ataxia; 1 - moderate ataxia, able to walk; 2 - severe ataxia, risk of laying down. To evaluate analgesia, the method was adapted from Figueiró et al. (2016). As such, two electrodes, placed five cm apart from each other, were fixed to the previously shaved skin of the pastern of the left thoracic limb, and were connected to an electric stimulator. Each stimulus (30 Hz, 400 μs) was applied by increasing the constant current (in mA) until a positive response was observed. Three observers evaluated the response via direct visual observation. In case of disagreement between the three observers, the noted response was discarded and the stimulus repeated. Prior to administration of the sedative (T0), the response threshold for each animal was detected, determining the lowest intensity (mA) electrical current capable of producing the response, that is, the lifting of the animal’s paw. After administration of the sedative, in each experimental moment, a new stimulation was performed, initially with an electric current that was slightly below the response threshold in T0, and increasing the milliamperage until the animal showed a response similar to T0. The maximum applied voltage was 80 milliamperes, and this was considered the cut-off, regardless of whether or not a reaction to the stimulus was produced, to avoid tissue damage (Love et al., 2011).

Heart rate (HR) was measured (bpm), calculated from the R-R interval obtained on a computerized electrocardiogram machine, using derivation DII, and velocity at 25 mm/second. For electrocardiography, the adhesive electrodes were positioned in previously shaved cutaneous areas, in a “base-apex” position, according to the following description: “right arm” electrode at the right jugular sulcus, “left arm” electrode at the fifth left intercostal space, and the “left leg” electrode positioned over the left scapula. Any arrhythmias were registered. Other measurements included: respiratory rate (RR) (mpm), via observation of the movements of the rib cage during one minute; rectal temperature (RT) (°C), using a digital clinical thermometer; blood glucose levels (G) (g/dL) measured using a portable glucometer, using a drop of blood collected from an ear capillary; and mean arterial pressure (MAP) measured via a non-invasive oscillometric method, at the coccygeal artery. An 8-cm long cuff (equivalent to 40% of the circumference of the tail of equines, according to the method described by Parry, 1986) was positioned at the base of the tail. Three consecutive readings were performed during each measurement, and the mean of the three was registered as the final MAP value. The measuring device for arterial pressure used in this study has not been validated for donkeys. Micturition frequency was also noted, as well as any observed changes.

All parameters were evaluated immediately before (T0) and five minutes after (T5) administration of the drug, every 10 minutes after administration for one hour (T10; T20; T30; T40; T50; T60), and every 15 minutes after T60 for two hours (T75; T90; T105; T120; T135; T150; T165; T180). Blood glucose levels were measured only at T0, T60, T120, and T180.

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1 Medcir MT-10 (Medical Cirurgica Ltda., Brazil).
2 ECGPC version 1.10 (Tecnologia Eletrônica Brasileira Ltda., Brazil).
3 Adhesive electrode for electrocardiography model 2223 (3M, Brazil Ltda).
4 Digital Clinical Thermometer (TH186-G - Tech, Brazil).
5 OnCall Plus (ACON Laboratories Inc., USA).
6 Portable non-invasive pressure meter - DL1100 (Deltalife, Brazil).
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None of the evaluators knew which treatment had been administered. Intensity of the sedation was evaluated by only one investigator during the entire experiment. Physiologic variables were measured by two evaluators before any stimuli were applied, to avoid influences on these parameters. Firstly, the main investigator evaluated HR and RR during one minute. Afterwards, an assistant investigator registered the MAP and the RT. Then blood glucose and the degree of analgesia and, later, the animal was removed from the stock for evaluation of ataxia.

Statistical analysis was done in a microcomputer, using GraphPad Prism 6.01 software. Analysis of the normality of the data was done via the Shapiro-Wilks test and concluded that all data evaluated were non-parametric. For comparison between groups, Kruskal Wallis with post hoc Student-Newman-Keuls (SNK) was used. For comparison of the moments, the Friedman test with post hoc SNK was performed. Significance level was set at 5%.

Results and discussion

The sedation caused by both drugs was characterized by low head carriage, labial and palpebral ptosis, somnolence, inspiratory sounds, and lowering of the ears. There was no significant difference between the groups regarding the latency period of the sedation (Table 1), showing that detomidine and xylazine have the same onset of action, even when given at different doses.

The sedation period was greater in the animals that were given detomidine when compared to those that received xylazine; however, there was no significant difference observed between the three administered doses of each drug (Table 1). This shows that, in the present study, increasing the dose of these drugs did not influence the duration of the sedation, as opposed to what happens in equines in general, where an increase in the dose of alpha2-adrenergic agonist prolonged its duration (Ringer et al., 2012b). Lizarraga & Beths (2012) demonstrated that xylazine produces less sedative effects in donkeys when compared with equines. It is thought that the sedative effect of xylazine in this study may have been masked by the small variation in doses. Detomidine had a greater sedative potency when compared to xylazine, as occurs in equines (Ramsay et al., 2002). According to Joubert et al. (1999), in donkeys, higher doses are needed to result in the same sedative effects seen in horses.

### Table 1. Median (± Semi-interquartile range) of the latency and duration, in minutes, of the sedative effect produced by detomidine and xylazine, given intravenously in different doses, in donkeys from northeast Brazil.

| Evaluation/Groups | XYLAZINE | DETOMIDINE |
|-------------------|----------|------------|
|                   | GX0.8    | GX1.0      | GX1.2      | GD0.02 | GD0.04 | GD0.06 |
| Latency           | 0.83 (±19)| 1.0 (±15)  | 1.0 (±13)  | 0.66 (±11)| 0.83 (±11)| 0.50 (±11)|
| Duration          | 42 (±10)^a| 45 (±16)^b | 47 (±12)^b | 115 (±26)^b| 92 (±33)^b| 140 (±36)^b|

^a, b = different letters indicate a significant difference between groups (p<0.05).

It was observed that, in groups GX0.8, GX1.0, and GX1.2, the lower lip-ground distance significantly decreased after T5, remaining low until T30 in the first two groups and until T40 in GX1.2 (Table 2). However, in detomidine groups, there was a significant decrease in lower lip-ground distance from T5 to T60 in GD20 and to T75 in groups GD40 and GD60, with the nose-ground distance significantly lower until T90 in these groups when compared to xylazine groups. In other moments when there was a difference between the groups of two drugs, it was possible to observe that, when using the lower doses of detomidine, the nose-ground distance was similar to that observed with the greater doses of xylazine, showing that detomidine resulted in a more intense sedation due to its greater selectivity regarding adrenoceptors when compared to xylazine (Hubbell et al., 2012). Xylazine has a selectivity ratio of 160 (Guirro et al., 2009) and detomidine of 260 (Fischer et al., 2009) between α-2/α-1 receptors, thus detomidine has similar action to xylazine, but with ten times the potency and longer lasting effects (Hubbell et al., 2012).
Ataxia occurred in every group, starting at T5, and lasting until T10 in GX0.8 and GX1.2, until T20 in GX1.0 and GD20, until T40 in GD40, and until T75 in GD60 (Table 3). Ataxia was more pronounced in groups GD40 and GD60 compared to GX0.8 and GX1.2 at T5; compared to GX0.8 at T40, and compared to GX0.8, GX1.0, and GX1.2 at T60. At T50, ataxia in groups GD20, GD40, and GD60 was more pronounced than in GX0.8 and GX1.2. At T75 and T90, ataxia in GD60 was more pronounced than in all other groups, except GD40. It is thus noticeable that detomidine, especially in higher doses, causes a more pronounced ataxia than xylazine. El-Kammar & Gad (2014) observed classical signs of ataxia in asinines with detomidine after 15 minutes of injecting the drug. These results reinforce the direct relationship of the sedative effects of these drugs and ataxia (Zeiler, 2015). Also, most studies evaluating the sedative effects of these drugs on equids have cited the degree of ataxia as one of the main variables used (Ringer et al., 2013; Gozalo-Marcilla et al., 2015; Lizarraga & Castillo-Alcala, 2015; Lizarraga et al., 2015; Gozalo-Marcilla et al., 2017).

The response threshold to electrostimulation was the same in all groups (Table 4). In all treatments, the level of electrostimulation increased after T5 and remained higher than baseline until T10 in groups GX0.8, GX1.0, and GX1.2. It is thus suggested that the analgesia produced by xylazine lasted only 10 minutes. In groups GD20 and GD40, there was statistical difference from T0 to T10, and in group GD60, until T30. This findings disagrees with Kamerling et al. (1988), who stated that the duration of analgesia produced by xylazine and detomidine is dose-dependent. Detomidine had a greater analgesic effect at a dose of 60 μg/kg, reaching 30 minutes, when compared to other groups. Techniques that use an electric current to generate a nociceptive stimulus are widely used in evaluating analgesia in equines. With some variation in models, these techniques basically consist in measuring the lowest electrical current capable of producing an averse response (Love et al., 2011). This type of stimulus has some advantages over other techniques to evaluate antinociception, since its quantification, standardization, and reproduction are easily obtained (Le Bars et al., 2001). Nevertheless, it is still questionable whether a supramaximal stimulus is needed to guarantee the repeatability of the stimulation (Eger 2nd et al., 2008) and whether the animal can become accustomed to the stimulus (Laster et al., 1993), which may have happened in the present study.

Table 2. Median (± Semi-interquartile range) of the nose-ground distance (cm) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE | DETOMIDINE |
|--------------|----------|------------|
|              | GX0.8    | GX1.0      | GX1.2      | GDO.02  | GDO.04  | GDO.06  |
| T0           | 71 (±5)  | 74 (±8)    | 72 (±6)    | 67 (±7) | 72 (±6) | 74 (±9) |
| T5           | 19 (±11) | 6 (±5)*    | 6 (±6)*    | 2 (±4)* | 4 (±5)* | 11 (±9)*|
| T10          | 16 (±7)* | 6 (±3)*    | 14 (±7)*   | 6 (±6)* | 6 (±6)* | 12 (±7)*|
| T20          | 19 (±9)* | 16 (±7)*   | 17 (±12)*  | 9 (±6)* | 4 (±9)* | 18 (±15)*|
| T30          | 25 (±10)*| 32 (±24)*  | 24 (±15)*  | 10 (±19)*| 4 (±9)* | 20 (±6)*|
| T40          | 67 (±6)* | 59 (±26)*  | 42 (±17)** | 19 (±15)*| 18 (±15)*| 12 (±7)*|
| T50          | 68 (±7)* | 60 (±19)*  | 62 (±10)*  | 12 (±22)**| 20 (±9)* | 15 (±17)**|
| T60          | 70 (±9)* | 64 (±16)*  | 63 (±12)*  | 39 (±14)**| 20 (±9)* | 25 (±23)**|
| T75          | 75 (±11)*| 63 (±22)** | 73 (±7)*   | 40 (±14)*| 27 (±18)*| 30 (±16)**|
| T90          | 71 (±7)* | 66 (±13)** | 73 (±6)*   | 54 (±10)*| 46 (±15)*| 46 (±14)*|
| T105         | 69 (±3)* | 73 (±10)** | 65 (±5)**  | 62 (±8)**| 54 (±14)*| 34 (±20)*|
| T120         | 74 (±7)* | 71 (±11)*  | 74 (±7)*   | 56 (±12)**| 57 (±12)*| 54 (±15)*|
| T135         | 71 (±7)* | 67 (±7)*   | 65 (±4)*   | 58 (±6)**| 59 (±9)* | 61 (±16)*|
| T150         | 75 (±5)* | 70 (±11)*  | 71 (±3)*   | 62 (±10)**| 62 (±11)*| 50 (±11)*|
| T165         | 75 (±4)* | 73 (±7)*   | 70 (±5)**  | 68 (±8)**| 54 (±11)*| 59 (±8)* |
| T180         | 77 (±6)* | 65 (±8)    | 74 (±4)    | 73 (±9)  | 63 (±14) | 59 (±9)  |

a, b, ab = different letters indicate a significant difference between groups in each moment (p<0.05). * = significant difference between that moment and T0 (p<0.05).
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Table 3. Median (±: Semi-interquartile range) degree of ataxia in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYL AZINE | DETOMIDINE |
|--------------|-----------|------------|
|              | GX0.8     | GX1.0      | GX1.2      | GDO.02     | GDO.04     | GDO.06     |
| T0           | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T5           | 1.0 (±0.1)* | 1.5 (±0.2)* | 1.0 (±0.0)* | 1.5 (±0.2)* | 2.0 (±0.0)* | 2.0 (±0.2)* |
| T10          | 1.0 (±0.1)* | 1.5 (±0.2)* | 1.0 (±0.0)* | 1.5 (±0.2)* | 2.0 (±0.0)* | 2.0 (±0.2)* |
| T20          | 1.0 (±0.3) | 1.0 (±0.2) | 1.0 (±0.1) | 1.0 (±0.2) | 1.0 (±0.2) | 1.0 (±0.2) |
| T30          | 0.5 (±0.1) | 1.0 (±0.2) | 1.0 (±0.1) | 1.0 (±0.1) | 1.0 (±0.1) | 1.0 (±0.1) |
| T40          | 0.0 (±0.1)* | 0.0 (±0.2)* | 0.5 (±0.5)* | 1.0 (±0.3)* | 0.5 (±0.5)* | 1.0 (±0.3)* |
| T50          | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T60          | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T70          | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T90          | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T105         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T120         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T135         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T150         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T165         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |
| T180         | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) | 0.0 (±0.0) |

* = significant difference for the moment compared to T0 (p<0.05).

Table 4. Median (±: Semi-interquartile range) electrostimulation (milliamperes) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYL AZINE | DETOMIDINE |
|--------------|-----------|------------|
|              | GX0.8     | GX1.0      | GX1.2      | GDO.02     | GDO.04     | GDO.06     |
| T0           | 17 (±20)  | 8 (±5.4)   | 11 (±16)   | 17 (±7)    | 8 (±15)    | 8 (±6)     |
| T5           | 42 (±11)* | 34 (±10.8)* | 26 (±17)* | 49 (±23)*  | 56 (±23)*  | 33 (±13)*  |
| T10          | 40 (±9)*  | 40 (±11)*  | 26 (±16)* | 44 (±18)*  | 44 (±23)*  | 34 (±4)*   |
| T20          | 36 (±9)   | 31 (±12)   | 26 (±13)   | 35 (±13)   | 40 (±25)   | 35 (±4)*   |
| T30          | 33 (±18)  | 28 (±17)   | 21 (±13)   | 29 (±22)   | 40 (±21)   | 33 (±6)*   |
| T40          | 29 (±15)  | 22 (±14)   | 8 (±6)     | 31 (±13)   | 37 (±22)   | 26 (±14)   |
| T50          | 26 (±20)  | 17 (±13)   | 8 (±6)     | 34 (±11)   | 36 (±19)   | 27 (±13)   |
| T60          | 28 (±12)  | 17 (±13)   | 8 (±6)     | 22 (±13)   | 40 (±20)   | 26 (±5)    |
| T70          | 14 (±16)  | 8 (±7)     | 8 (±5)     | 31 (±9)    | 22 (±19)   | 26 (±10)   |
| T90          | 23 (±15)  | 8 (±6)     | 8 (±5)     | 21 (±11)   | 29 (±17)   | 22 (±13)   |
| T105         | 18 (±15)  | 8 (±3)     | 7 (±6)     | 21 (±11)   | 23 (±16)   | 27 (±15)   |
| T120         | 18 (±14)  | 8 (±2)     | 5 (±8)     | 20 (±11)   | 23 (±13)   | 26 (±11)   |
| T135         | 14 (±14)  | 8 (±2)     | 5 (±6)     | 16 (±12)   | 23 (±18)   | 21 (±10)   |
| T150         | 11 (±14)  | 8 (±4)     | 5 (±6)     | 16 (±11)   | 19 (±15)   | 17 (±11)   |
| T165         | 11 (±15)  | 8 (±4)     | 7 (±6)     | 15 (±7)    | 20 (±16)   | 14 (±11)   |
| T180         | 11 (±10)  | 8 (±4)     | 7 (±5)     | 16 (±9)    | 14 (±12)   | 17 (±10)   |

* = significant difference for the moment compared to T0 (p<0.05).
There was no significant difference in HR either within or between groups (Table 5) in the animals receiving xylazine. However, in the groups receiving detomidine, there was a significant decrease at T60, T75, T105, T120, and T165 in group GD20 and from T165 to T180 in group GD40, with no statistical difference between groups. Therefore, with the doses used in the present study, xylazine produced less changes in HR than detomidine. Regarding the cardiovascular system, alpha2-agonists lead to inhibition of the sympathetic tone due to the decreased pre-synaptic release of noradrenaline, which causes a decrease in heart rate (Murrell & Hellebrekers, 2005).

Regarding cardiac changes observed in the different studied groups, it was observed that 16.7% of animals in groups GX0.8 and GX1.0, and 33.3% of group GX1.2 had Mobitz type 2 or 1st degree atrioventricular blocks (AVB), with type 2 diagnosed in 50%, 16.7%, and 16.7% of animals in groups GX0.8, GX1.0, and GX1.2, respectively. In groups GD20, GD40, and GD60, Mobitz type 2 or 1st degree AVB were detected in 16.7%, 33.3%, and 50% of animals, respectively, with 83.3% of arrhythmias in the three groups being Mobitz type 2 or 1st degree AVB. One of the more commonly observed cardiovascular effects after administration of alpha2-adrenergic agonists is AVB, due to the increase in parasympathetic tone. These arrhythmias are tolerated in equines with normal heart function (Ringer et al., 2012a).

Table 5. Median (± Semi-interquartile range) heart rate (bpm) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE | DETOMIDINE |
|--------------|----------|------------|
|              | GX0.8    | GX1.0      | GX1.2      | GDO.02 | GDO.04 | GDO.06 |
| T0           | 40 (±14) | 41 (±16)   | 39 (±9)    | 41 (±7) | 39 (±7) | 49 (±12) |
| T5           | 39 (±7)  | 39 (±7)    | 35 (±7)    | 36 (±4) | 38 (±6) | 38 (±7) |
| T10          | 35 (±6)  | 38 (±9)    | 34 (±8)    | 34 (±3) | 33 (±7) | 37 (±4) |
| T20          | 36 (±6)  | 40 (±7)    | 38 (±5)    | 33 (±3) | 34 (±5) | 36 (±3) |
| T30          | 38 (±8)  | 42 (±10)   | 40 (±7)    | 34 (±4) | 33 (±5) | 34 (±6) |
| T40          | 38 (±9)  | 46 (±10)   | 38 (±7)    | 34 (±3) | 33 (±6) | 35 (±4) |
| T50          | 40 (±8)  | 47 (±10)   | 40 (±8)    | 35 (±5) | 33 (±5) | 35 (±7) |
| T60          | 38 (±8)  | 46 (±8)    | 39 (±7)    | 33 (±4)* | 33 (±5) | 37 (±5) |
| T75          | 37 (±9)  | 39 (±8)    | 37 (±7)    | 32 (±5)* | 33 (±6) | 36 (±7) |
| T90          | 38 (±11) | 41 (±10)   | 35 (±7)    | 33 (±4) | 36 (±8) | 37 (±7) |
| T105         | 39 (±8)  | 42 (±8)    | 36 (±7)    | 32 (±4)* | 38 (±9) | 33 (±7) |
| T120         | 40 (±8)  | 41 (±7)    | 35 (±8)    | 32 (±5)* | 36 (±8) | 35 (±6) |
| T135         | 39 (±8)  | 42 (±12)   | 35 (±9)    | 34 (±6) | 36 (±6) | 34 (±7) |
| T150         | 37 (±9)  | 43 (±11)   | 36 (±8)    | 35 (±6) | 33 (±7) | 36 (±5) |
| T165         | 37 (±8)  | 47 (±12)   | 36 (±7)    | 32 (±6)* | 32 (±8)* | 33 (±7) |
| T180         | 39 (±9)  | 46 (±13)   | 37 (±6)    | 34 (±6) | 31 (±6)* | 35 (±6) |

* = significant difference for the moment compared to T0 (p<0.05).

Starting at T90, RR was greater in some groups that received xylazine when compared to some of the detomidine groups. This is probably because of the shorter duration of the sedation caused by xylazine compared to detomidine, where the return to normal cognition may have led to an increase in stress from being contained in the stock and evaluation of parameters. The RR decreased between T10 and T40 in GX0.8, from T30 to T75 in GX1.0 and only at T20 and T40 in GX1.2 when compared to the baseline value. On the other hand, in the groups receiving detomidine, there was a decrease in RR when compared to the baseline value at from T75 to T120, at T150, and at T180 in group GD20, at T105 and T165 in GD40, and at T105 and between T135 and T165 in GD60 (Table 6). Despite the decrease in f values remained within the normal range, which is between 16 and 66 ppm (Simenew et al., 2011), in all groups during most of the moments. This decrease in RR was apparently due to sedation caused by the administered drugs, even in the moments when this parameter was below the reference value for the species.
Detomidine and xylazine, at different doses, in donkeys (Equus asinus)

Table 6. Median (± semi-interquartile range) respiratory rate (mpm) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE | DETOMIDINE |
|--------------|----------|------------|
|              | GX0.8    | GX1.0      | GX1.2      |
| T0           | 38 (±16) | 28 (±18)   | 32 (±13)   |
| T5           | 20 (±5)  | 25 (±5)    | 19 (±7)    |
| T10          | 16 (±3)* | 22 (±5)    | 20 (±6)    |
| T20          | 16 (±4)* | 17 (±4)    | 17 (±7)*   |
| T30          | 14 (±5)* | 19 (±4)*   | 18 (±6)    |
| T40          | 20 (±5)* | 16 (±7)*   | 14 (±5)*   |
| T50          | 22 (±6)  | 16 (±5)*   | 18 (±13)   |
| T60          | 22 (±8)  | 15 (±5)*   | 19 (±8)    |
| T75          | 20 (±10) | 16 (±6)*   | 20 (±8)    |
| T90          | 20 (±7) ab| 20 (±11) ab| 26 (±9) a  |
| T105         | 24 (±12) a| 30 (±17) a| 24 (±9) a  |
| T120         | 26 (±12) a| 20 (±8) ab| 21 (±7) a  |
| T135         | 26 (±12) a| 17 (±12) ab| 25 (±8) a  |
| T150         | 26 (±8) a| 25 (±9) a  | 21 (±8) a  |
| T165         | 24 (±8) a| 27 (±9) a  | 28 (±9) a  |
| T180         | 32 (±5) a| 23 (±10) a| 26 (±7) a  |

|              | GDO0.2   | GDO0.4     | GDO0.6     |
|--------------|----------|------------|------------|
| T0           | 22 (±7)  | 25 (±15)   | 25 (±8)    |
| T5           | 23 (±9)  | 24 (±9)    | 23 (±8)    |
| T10          | 24 (±8)  | 24 (±6)    | 26 (±4)    |
| T20          | 24 (±9)  | 20 (±7)    | 23 (±7)    |
| T30          | 24 (±7)  | 22 (±6)    | 27 (±6)    |
| T40          | 19 (±10) | 18 (±6)    | 21 (±7)    |
| T50          | 15 (±6)  | 16 (±4)    | 22 (±7)    |
| T60          | 18 (±5)  | 14 (±6)    | 20 (±4)    |
| T75          | 12 (±4)* | 15 (±4)    | 19 (±5)    |
| T90          | 14 (±5) ab| 13 (±2) b  | 19 (±4) ab |
| T105         | 12 (±8) a| 12 (±2) b  | 15 (±4) a  |
| T120         | 16 (±3) a| 12 (±2) b  | 17 (±3) ab |
| T135         | 17 (±5) ab| 14 (±3) b  | 14 (±2) a  |
| T150         | 14 (±5) ab| 12 (±3) b  | 12 (±3) a  |
| T165         | 16 (±3) ab| 11 (±2) ba | 14 (±3) a  |
| T180         | 16 (±1) ba| 12 (±1) b  | 16 (±4) b  |

a, b, ab = different letters indicate a significant difference between groups for each moment (p<0.05). * = significant difference for the moment compared to T0 (p<0.05).

All animals in the study had their rectal temperature below the minimum physiological limits for asinines, which is 37.5°C (Simenew et al., 2011) at the basal moment (T0) (Table 7). This was because the thermometer used was shorter and thus only measured the temperature at the most caudal portion of the rectum, which, because of the anal sphincter, suffers influence from the ambient temperature. The animals that received detomidine had a decrease in rectal temperature from T90 in GD20 and from T105 in GD40 and GD60 until the end of the experimental period, with significantly lower temperatures when compared to those of the xylazine group, starting at T120. Among the xylazine groups, the TR was significantly reduced only at T75 and T90 in relation to T0 in GX1.2; in all other moments, the temperature increased. It is thought that the method for measuring temperature in the present study was not adequate for the studied species.

Regarding blood glucose levels, in the xylazine groups, 60 minutes after administration of the sedative, there was a significant statistical difference in GX0.8 and GX1.0 compared to the basal moment; without differences between groups (Table 8). Hyperglycemia was not present in any group that received xylazine, and blood glucose levels remained within normal standards for asinines, i.e. between 44 and 90 mg/dL (Mori et al., 2003). Blood glucose levels remained elevated (compared to basal values) until two hours after administration of detomidine in groups GD40 and GD60 and until one hour in GD20, with the presence of hyperglycemia. Blood glucose levels were significantly higher in groups GD40 and GD60 when compared to xylazine groups, suggesting that detomidine has a greater hyperglycemic effect, especially at higher doses. The increase in blood glucose levels after administration of alpha2-adrenergic agonists occurs due to inhibition of insulin secretion mediated by the stimulation of alpha2-adrenoceptors in the pancreas (Ambrósio et al., 2012).

Mean amount of micturitions during the experimental period was 0.8, 0.8, 1.2, 1.8, 2.0, and 2.2 respectively for groups GX0.8, GX1.0, GX1.2, GD20, GD40, and GD60, with differences only between groups GX0.8 and GD60. It was observed that the higher micturition frequencies in the detomidine groups coincided with the higher levels of glucose. The increase in micturition frequency is caused by inhibition of the antidiuretic hormone and renin, increasing the glomerular filtration rate and release of atrial natriuretic peptide. Also, hyperglycemia results in osmotic diuresis (El-Maghraby et al., 2005).
Detomidine and xylazine, at different doses, in donkeys (*Equus asinus*).

Table 7. Median (± Semi-interquartile range) rectal temperature (°C) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE       | DETOMIDINE     |
|--------------|----------------|----------------|
|              | GX0.8 | GX1.0 | GX1.2 | GDO.02 | GDO.04 | GDO.06 |
| T0           | 37 (±0.5) | 37 (±0.6) | 37 (±0.1) | 37 (±0.3) | 37 (±0.5) | 37 (±0.5) |
| T5           | 37 (±0.5) | 37 (±0.6) | 37 (±0.6) | 37.5 (±0.5) | 37 (±0.5) | 37.5 (±0.5) |
| T10          | 37 (±0.5) | 37 (±0.6) | 37 (±0.5) | 37 (±0.5) | 37 (±0.3) | 37 (±0.5) |
| T20          | 37 (±0.1) | 37 (±0.6) | 37 (±0.5) | 37.5 (±0.5) | 37 (±0.6) | 37.5 (±0.5) |
| T30          | 37 (±0.1) | 37 (±0.6) | 37 (±0.1) | 37 (±0.1) | 37 (±0.5) | 37 (±0.5) |
| T40          | 37 (±0.1) | 37 (±0.3) | 37 (±0.3) | 37 (±0.6) | 37 (±0.1) | 37 (±0.5) |
| T50          | 37 (±0.0) | 37 (±0.4) | 37 (±0.5) | 37 (±0.6) | 37 (±0.1) | 37 (±0.5) |
| T60          | 37 (±0.5) | 37 (±0.6) | 37 (±0.5) | 37 (±0.6) | 37 (±0.0) | 37 (±0.5) |
| T75          | 37 (±0.1) | 37 (±0.8) | 36.5 (±0.6) | 37 (±0.6) | 37 (±0.5) | 36.5 (±0.5) |
| T90          | 36.5 (±0.6) | 37 (±0.6) | 36.5 (±0.5) * | 36.5 (±0.5) * | 36 (±0.5) | 36 (±0.5) |
| T105         | 37 (±0.1) | 36.5 (±0.8) | 37 (±0.5) | 36.5 (±0.5) * | 36 (±0.1) * | 36 (±0.5) * |
| T120         | 37 (±0.3) & | 37 (±0.6) ab | 37 (±0.5) a | 36 (±0.5) ** | 36 (±0.1) ** | 36 (±0.5) a |
| T135         | 37 (±0.5) b | 37 (±0.6) ab | 37 (±0.5) b | 36 (±0.6) ** | 36 (±0.1) ** | 36 (±0.5) b |
| T150         | 37 (±0.5) a | 37 (±0.3) a | 37 (±0.1) a | 36 (±0.3) ** | 36 (±0.3) ** | 36 (±0.5) a |
| T165         | 37 (±0.5) a | 37 (±0.6) a | 37 (±0.1) a | 36 (±0.3) ** | 35.5 (±0.5) ** | 35.5 (±0.5) a |
| T180         | 37 (±0.5) a | 37 (±0.5) a | 37 (±0.1) a | 36 (±0.5) ** | 36 (±0.6) ** | 36 (±0.5) a |

a, b, ab = different letters indicate a significant difference between groups for each moment (p<0.05). * = significant difference for the moment compared to T0 (p<0.05).

Table 8. Median (± Semi-interquartile range) blood glucose (g/dL) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE       | DETOMIDINE     |
|--------------|----------------|----------------|
|              | GX0.8 | GX1.0 | GX1.2 | GDO.02 | GDO.04 | GDO.06 |
| T0           | 67 (±8) | 77 (±9) | 81 (±9) | 65 (±7) | 72 (±5) | 73 (±3) |
| T60          | 80 (±6) a | 84 (±21) ab | 86 (±12) a | 119 (±13) a | 144 (±7) ab | 167 (±18) a |
| T120         | 73 (±5) a | 75 (±12) a | 75 (±9) a | 98 (±17) a | 117 (±22) a | 139 (±36) a |
| T180         | 72 (±2) a | 73 (±9) a | 74 (±9) a | 85 (±12) a | 94 (±12) b | 103 (±29) a |

a, b, ab = different letters indicate a significant difference between groups for each moment (p<0.05). * = significant difference for the moment compared to T0 (p<0.05).

In the groups that received xylazine, mean arterial pressure was significantly decreased only at T50 in GX1.0 and at T40 in GX1.2. However, in groups GD20, GD40, and GD60, the MAP increased at T5, and remained elevated until T20, T30, and T10, respectively. Mean arterial blood pressure in adult equids vary between 110 and 133 mmHg (Magdesian, 2004), however, values above 60 mmHg are considered adequate to maintain cardiac output and tissue perfusion. Therefore, there was no hypo or hypertension in either group when considering the mean values recorded. There was a statistical difference between the dose groups for each sedative; however, the MAP of the groups that received detomidine was higher than the xylazine groups in several experimental moments (Table 9). The increase in arterial pressure caused by these drugs is attributed to the peripheral post-synaptic alpha-adrenergic stimulation which results in peripheral vasoconstriction (Ringer et al., 2012a). In the present study, the effects of detomidine on MAP were more marked than that of xylazine.
Table 9. Median (± semi-interquartile range) mean arterial pressure (mmHg) in donkeys from northeast Brazil sedated with detomidine or xylazine, given intravenously in different doses.

| Times/Groups | XYLAZINE | DETOMIDINE |
|--------------|----------|------------|
|              | GX0.8    | GX1.0      | GX1.2      | GDO.02   | GDO.04   | GDO.06   |
| T0           | 64 (±16) | 77 (±5)    | 81 (±17)   | 71 (±8)  | 71 (±11) | 78 (±10) |
| T5           | 94 (±15) | 94 (±11)   | 108 (±12)  | 126 (±22)| 117 (±9) | 131 (±18)|
| T10          | 77 (±8)  | 76 (±11)   | 88 (±14)   | 108 (±15)| 109 (±17)| 119 (±21)|
| T20          | 62 (±7)  | 79 (±18)   | 77 (±21)   | 106 (±27)| 107 (±12)| 116 (±26)|
| T30          | 69 (±11) | 79 (±20)   | 65 (±10)   | 99 (±19)| 105 (±14)| 108 (±19)|
| T40          | 65 (±11) | 66 (±19)   | 62 (±6)    | 85 (±22)| 94 (±13)| 103 (±16)|
| T50          | 62 (±10) | 64 (±6)    | 64 (±5)    | 82 (±25)| 94 (±15)| 103 (±20)|
| T60          | 73 (±14) | 67 (±8)    | 78 (±17)   | 73 (±21)| 89 (±15)| 94 (±5)  |
| T75          | 65 (±8)  | 74 (±16)   | 74 (±6)    | 85 (±13)| 88 (±22)| 92 (±18)|
| T90          | 77 (±13) | 73 (±9)    | 71 (±7)    | 85 (±18)| 84 (±18)| 80 (±13)|
| T105         | 78 (±18) | 72 (±3)    | 81 (±16)   | 82 (±13)| 78 (±12)| 76 (±11)|
| T120         | 74 (±6)  | 75 (±9)    | 73 (±8)    | 73 (±12)| 78 (±17)| 74 (±10)|
| T135         | 75 (±8)  | 73 (±4)    | 76 (±11)   | 78 (±12)| 87 (±18)| 75 (±10)|
| T150         | 74 (±6)  | 77 (±6)    | 81 (±15)   | 72 (±10)| 80 (±20)| 77 (±13)|
| T165         | 69 (±6)  | 77 (±7)    | 77 (±16)   | 77 (±13)| 72 (±12)| 76 (±7)  |
| T180         | 87 (±14) | 75 (±11)   | 73 (±10)   | 77 (±3) | 78 (±18)| 74 (±7)  |

a, b, ab = different letters indicate a significant difference between groups for each moment (p<0.05). * = significant difference for the moment compared to T0 (p<0.05).

During the experimental period, all animals sneezed for a mean of six, 15, and 40 minutes in groups GX0.8, GX1.0, and GX 1.2, respectively, and 16, 19, and 93 in groups GD20, GD40, and GD60, respectively. The longest duration was in animal five of group GD60: 150 minutes. Aside from sneezing, intense itching on the nose and inspiratory sounds were also observed in 92% of the animals in all groups. These reactions may be associated with the prolonged period of lower head carriage in conjunction with relaxation of the superior airways. There was penile relaxation in all animals, starting at a mean of 123 ± 83 seconds after administration of the sedatives and lasting 75 ± 39 minutes, with no statistical difference between groups. One of the more noticeable effects of xylazine and detomidine in equids is penile exposure which, along with other changes such as labial and palpebral ptosis and ataxia, occurs because of stimulation of pre-synaptic α-2 adrenergic receptors, which modulate the sympathetic activity of the autonomous nervous system (Ringer et al., 2012b).

Conclusion

In donkeys, xylazine and detomidine produce short-term analgesia and discreet cardiorespiratory changes. These two alpha2-adrenergic agonists are therefore safe and effective to use in the tested doses in sedation protocols in standing donkeys.

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