CLINICAL AND SAFETY EVALUATION OF A READY-TO-USE GUAYACOL GLYCERYL ETHER (RTU-GGE) LIQUID SOLUTION IN HORSES

AVALIAÇÃO DA SEGURANÇA E EFICÁCIA CLÍNICA DE UMA SOLUÇÃO LÍQUIDA DE ÉTER GLICERIL GUAIACOL PRONTA PARA USO (EGG-RTU) EM CAVALOS

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SUMMARY

The main objective of this study was to evaluate the clinical efficiency and safety of a 10% ready for use GGE solution (RTU-GGE) after intravenous injection in horses. The compatibility of the EGG-RTU solution with xylazine and ketamine and its cardiorespiratory effects were also evaluated. Four equines received the conventional GGE solution prepared just before the use (EGG group); 21 days later, the animals received the EGG-RTU solution (RTU group); and after a new period of 21 days, the equines received the EGG-RTU solution associated with ketamine and xylazine (TD group). Heart and respiratory rates, pulse oxymetry, mean arterial pressure and rectal temperature were evaluated. The time of administration of the solutions; the latency for recumbency; the time between the end of the administration of the solutions and the sternal recumbency; and the time between the end of the administration of solutions and the regain of quadrupedal position were registered. Finally, the EGG-RTU formulation developed for anesthesia of large animals is presented, as well as its clinical efficiency and pharmacological evaluation. We concluded that the EGG-RTU solution is efficient and safe for chemical restraint of horses and is compatible with ketamine and xylazine for intravenous anesthesia in this species.

KEY-WORDS: Efficacy. Horses. Guaiphenesin. Intravenous anesthesia. Safety.

RESUMO

O principal objetivo deste estudo foi avaliar a eficiência clínica e a segurança da administração intravenosa de uma solução de EGG pronta para uso (EGG-RTU), na concentração de 10% em equinos. Também foram avaliados a compatibilidade do EGG-RTU com a xilazina e cetamina e os efeitos cardiorrespiratórios desta associação na anestesia de equinos. Quatro equinos foram submetidos ao protocolo experimental, uma vez empregando o EGG preparado de forma tradicional (grupo EGG), outra usando o EGG pronto para uso (grupo RTU) e outra usando a solução EGG-RTU em associação com cetamina e xilazina (grupo TD), com intervalos de 21 dias. Foram avaliadas as frequências cardíaca e respiratória, a saturação da oxihemoglobina, a pressão arterial média e a temperatura retal. Também foram registrados e comparados o tempo de administração das soluções; o período de latência para o decúbito; o tempo entre o final da administração das soluções e o momento em que os animais adotaram o decúbito esternal; e o tempo entre o final da administração e o momento em que os animais recuperaram a posição quadrupedal. Finalmente, foi apresentada a formulação desenvolvida para anestesia de grandes animais, bem como sua avaliação clínica e farmacológica. Concluiu-se que a solução injetável EGG-RTU é eficaz e segura para contenção química de equinos e apresenta compatibilidade com a cetamina e a xilazina para a manutenção da anestesia total intravenosa nesta espécie.

PALAVRAS-CHAVE: Anestesia intravenosa. Eficácia. Equinos. Guaifenesina. Segurança.

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INTRODUCTION

The increasing number of purebred and mestizo horses in Brazil, reared for many different purposes, is the reason behind market requirements for increasingly specialized management, coaching, facilities, food and mainly technical veterinarian services. Sometimes, horses need to undergo small and average surgical procedures and there is no possibility of transporting them to referral centers or teaching hospitals. In such cases, veterinarians would benefit from practical and safe good quality products that could be purchased at competitive prices.

Guaiacol glyceryl ether (GGE) is a centrally acting muscle relaxant commonly used in equine anesthesia. This substance produces muscle relaxation without affecting the diaphragm and, unlike the peripheral neuromuscular blockers does not require the use of intermittent positive pressure ventilation (Hall et al., 2001). However, the use of EGG as single agent is not suitable for surgical procedures, since the doses required to induce immobility are high and most importantly, have minimal sedative and analgesic effect (HUBELL, 1996).

Intravenous anesthesia in horses may be performed by associating GGE with ketamine and an alpha adrenergic receptor agonist-2 (xylazine or detomidine). This solution, known worldwide as Triple Drip contains 50-100 mg/mL EGG, 0.5-1 mg/mL xylazine and 1.4 mg/mL ketamine, all diluted in 0.9% saline or distilled water with 5% glucose. This combination allows maintaining surgical anesthesia when performing field procedures that last one to two hours, using continuous intravenous infusion rates ranging from 0.5 to 2.2 mL/ kg/h (YOUNG et al. 1,993 and TAYLOR et al. 1998).

Several studies have proven that horses undergoing general anesthesia using ketamine associations/detomidine/EGG, ketamine/romifidine/EGG or ketamine/xylazine/GGE showed less impairment of cardiorespiratory function than those anesthetized with halothane. In addition, there are reports that these intravenous total anesthesia techniques can suppress adrenocortical response, allow better tissue perfusion (by properly maintaining blood pressure and left ventricular function) and provide greater analgesia and reflex suppression, compared to halothane inhalational anesthesia (YOUNG et al. 1993; TAYLOR et al. 1998; MCMURPHY et al. 2002).

Currently, the national market does not have a ready for use GGE, since this product is commercialized as a powder to be diluted in previously heated sterile aqueous solutions. Although these solutions are apparently stable, they may precipitate; and sometimes, the veterinarian working in the field does not have appropriate conditions to prepare it, increasing the risks for the patient.

Thus, the main objective of this study was to evaluate the clinical effectiveness and any side effects of intravenous injection of a ready for use solution of guaiacol glyceryl ether (GGE-RTU), at 10% concentration in horses. We also evaluated the compatibility of the GGE-RTU with xylazine and ketamine and cardiorespiratory effect caused by this anesthesia association in horses.

MATERIAL AND METHODS

Developing the GGE-RTU solution

Ten test formulations were prepared using the following components: sodium metabisulfite, glucose, mannitol, benzyl alcohol, propylene glycol and water for injection in addition to the active ingredient, guaiphenesin. These formulations were prepared in a three-step process.

The first step consisted of preparing a series of ten aqueous solutions containing water soluble components that were obtained by dissolving glucose, different amounts of sodium metabisulfite and mannitol in water at room temperature. The ten vials containing the solutions were then labeled Phase A1 to Phase A10.

In the second step, a series of ten solutions, called B1 to B10 Phases were prepared by solubilizing benzyl alcohol (preservative and local anesthetic) in different volumes of propylene glycol (solvent).

The third step consisted of finalizing the test formulations. The solutions from Phases A1 to A10 were combined with the solutions from Phases B1 to B10, respectively, and mixed well by stirring with a glass rod. Subsequently, GGE was added to the solutions still under constant stirring, and these were heated at 70^{o}C until its complete solubilization.

After cooling, water for injection was added to the solutions to complete 100 mL final volume. These test formulations were labeled FT1 to FT10.

All FT were stored at 5^{o}C and checked visually every hour for the presence of precipitate, first against a white followed by black backgrounds, for up to 48 hours.

The cold precipitation test showed that all preparations with concentrations of propylene glycol less than 40% had precipitates in them. Therefore, pharmacologically only test formulations FT8, FT9 and FT10 with co-solvent concentrations of 40, 45 and 50%, respectively, were considered satisfactory. FT8 was chosen to be tested in the field among these three possibilities due to lower hemolytic potential resulting from the lower propylene glycol co-solvent concentration. Subsequently, it was requested to the Ministério da Agricultura, Pecuária e Abastecimento (MAPA), the regulator of pharmaceuticals for veterinary use, authorization to manufacture three pilot-scale batches corresponding to 10% of industrial capacity (process 21052.025240/2009-28), to ensure the similarity between batches, thus, ensuring the standardization of the process.

Upon completion of the similarity study, one of the three pilot batches was randomly chosen to determine product shelf life, by means of accelerated stability and long term studies. In the accelerated stability study, fifty samples were taken from the selected pilot batch, and placed in an acclimatization

chamber under forced storage conditions. The product was maintained at 40 ± 2°C, 75 ± 5% relative humidity for a period of six months. So, a provisional expiry date of 24 months was granted for substances that showed degradation equal to or less than 5%. In the accelerated stability study, we also determined:

a) Density and pH: at time zero, 1, 2, 3, and 6 months after the product was stored in the chamber;

b) Active principle by High Performance Liquid Chromatography (HPLC): at time zero, 1, 2, 3 and 6 months after the product was stored in the chamber;

c) Microbiological evaluation of sterility and pyrogen, before and six months after the product was stored in the chamber.

The long-term stability study was performed in a second acclimatization chamber, at the same time. The samples (20% of the pilot batch) were stored throughout the two years (24 months) granted until product expiration date in the acclimatization chamber at 30 ± 2°C and 65 ± 5% relative humidity. The following parameters were determined:

a) Density and pH: at 0, 1, 2, 3, 6, 9, 12, 18 and 24 months after storing the product in the acclimatization chamber;

b) active ingredient by HPLC: at initial time, 1, 2, 3, 6, 9, 12, 18 and 24 months after storing the product in the acclimatization chamber;

c) Microbiological sterility and pyrogen; at initial time, six and 24 months after storing the product in the acclimatization chamber.

Clinical trials in order to determine drug efficacy and safety started after the pharmaceutical product was approved. Further details about the manufacturing process of the solution are given in Marques Neto (2009). All tests performed during the product development stage followed the normative instructions of the Ministério da Agricultura, Pecuária e Abastecimento (MAPA) and the recommendations of the American Pharmacopoeia.

Clinical evaluation

Animals

The clinical efficacy and safety of the GGE-RTU solution was evaluated in four horses, three females and one male, between three and eight years old, 366.25 ± 17.97 kg average weight, considered healthy after physical examination and complete blood count. During the experimental phase the animals were kept in stalls and paddocks of the Hospital Veterinário of Universidade de Franca (UNIFRAN) where they were fed hay, balanced commercial feed and water *ad libitum*.

Experimental design

To test drug clinical efficiency, the horses underwent the following experimental protocol: the first time, using the GGE prepared the traditional way (GGE group); the second time, using the ready for use GGE (RTU group); and the third time, the ready for use (RTU) solution was administered to animals in the form of Triple drip, along with ketamine and xylazine, to assess its compatibility and safety when combined with these drugs. The experimental procedures were performed with an interval of at least 21 days. The active ingredient used was always the same, and at 99.74% level (Guaiacol Glyceryl Ether, Henrifarma Produtos Químicos e Farmacêuticos Ltda., lot no. 50.381, São Paulo, SP, Brazil).

Animal instrumentation

On the day of the experiment, after solid and water fasting for eight and four hours, respectively, the horses were taken to the anesthetic induction room. A 14G intravenous catheter (Cateter intravenoso ETFE Radiopaco, Nipro Medical Ltda., Sorocaba, SP, Brazil) was placed in the left jugular vein for substance administration. After local anesthesia with 1 mL of 2% lidocaine without epinephrine (Lidocaine Hydrochloride 2%, Hipolabor, Sabara, MG, Brazil), a 22G catheter was introduced (Cateter intravenoso ETFE Radiopaco, Nipro Medical Ltda., Sorocaba, SP, Brazil) in the transverse facial artery by percutaneous puncture. The catheter was connected to a blood pressure cuff (sphygmomanometer Becton Dickinson Surgical Ind. Ltda., São Paulo, SP, Brazil) through a plastic circuit filled with a solution containing 5,000 international units (IU) of heparin in 500 mL 0.9% saline solution to determine mean blood pressure (MBP) by the direct method, placing the liquid/air interface at the right atrium height. The computerized electrocardiograph electrodes (TEB ECG-PC Electrocardiogram Computer, Tecnologia Eletrônica Brasileira Ltda, São Paulo, SP, Brazil) were connected to the horse limbs to record the electrocardiogram in lead II.

Experimental Protocol

After recording baseline values, we administered 1 mg/kg xylazine (10% Sedomin®, König Laboratories Ltd. in Brazil, São Paulo, SP) intravenously (IV), as pre- anesthetic medication (PAM). Five minutes later, by bottle pressurization, the rapid IV infusion of a previously prepared 10% solution in 5% glucose solution (Fresenius Kabi Laboratories Ltd., São Paulo, SP, Brazil) started in the GGE group, and the ready for use solution (RTU) also at 10% in the RTU group. The 100 mg/kg GGE dose was administered at the end of infusion in both groups. The horses were placed in dorsal recumbency and remained so until they were able to recover the standing position.

After 21 days from the last experimental procedure, the horses were prepared in the same manner as in the first clinical trial to assess the administration effects of RTU solution combined with xylazine and ketamine, the intravenous anesthesia known as Triple Drip (TD group). To the ready for use GGE solution was added 0.5 mg/mL 10% xylazine and 2 mg/mL 10% ketamine (Ketamine®, Agener União Saúde Animal, Embu-Guaçu, SP, Brazil). The animals were pre-medicated with 1 mg/kg xylazine and, after five minutes, anesthesia was induced by IV administration of 0.1 mg/kg midazolam (15 mg Dormium®, União Química Farmacêutica Nacional,

Embu-Guaçu, São Paulo, Brazil) and 2 mg/kg ketamine as a bolus, associated in the same syringe. Immediately after recumbency we started the administration of the prepared solution at 2 mL/kg/hr rate during one hour.

Evaluated variables

Figure 1 shows the criteria used to evaluate the quality of induction and recovery from anesthesia.

We assessed heart rate (HR) by computerized electrocardiography; respiratory rate (RR) by observing rib cage movements; mean blood pressure (MBP) by the invasive method; rectal temperature (RT) using digital thermometer; and oxyhemoglobin saturation (Sp_{O2}), by pulse oximetry (BCI 3303 Hand-held pulse Oximeter, Smiths-Medical, Hythe, Kent, UK) with the infrared sensor positioned on the tongue.

The time elapsed between PAM and GGE administration, time of drug administration, the latency for recumbency, the time to sternal recumbency, and the elapsed time until the animals regained their quadrupedal position were all recorded.

Evaluation times

Variables were recorded prior to drug administration (T0), five minutes after xylazine administration (T5), immediately after recumbency (Trec) and 10, 20 and 30 minutes after GGE solution administration (T10, T20 and T30, respectively). In the TD group, cardiorespiratory variables were recorded every 10 minutes during triple drip infusion (T10, T20, T30, 40, T50 and T60, respectively).

Statistical analysis

The data from the experimental phase were statistically analyzed using the software Jandel SigmaStat for Windows. Kolmogorov-Smirnov test was used to verify the normality of data, which are presented as means ± standard deviations. Analysis of variance ANOVA one-way was used to detect significant differences in the means, followed by Tukey test for parametric data and the Kruskal-Wallis test followed by the Tukey test for nonparametric data. To detect differences over time within each group, ANOVA one-way was used for repeated measures followed by Tukey for parametric data and one-way analysis of variance for repeated scores (Friedman procedure), followed by Tukey test for nonparametric data. Differences were considered significant at $p \leq 0.05$.

RESULTS

No adverse reactions were observed after intravenous administration of ready for use (RTU) guaiacol glyceryl ether solutions, the GGE prepared solution or the combined RTU solution with ketamine and xylazine (TD). One animal in the GGE group, despite showing marked ataxia, was not lying after the end of solution administration. All animals recovered completely in the three clinical trials.

Administration time was longer in the RTU group compared with GGE group ($p<0.029$). The time to standing position recovery was longer in the TD group, but significantly ($p<0.02$) different from GGE only. All horses from GGE and RTU groups returned to standing position after a single attempt, showing no signs of muscle weakness, ataxia or excitement. On the other hand, from the TD group, one horse made two attempts; two horses made three attempts; while one animal, four attempts. Furthermore, the horses from this group showed ataxia during few minutes after recovering the standing position. Table 1 shows average time elapsed from pre-anesthesia medication (PAM) until standing position recovery.

Figure 1 - Criteria used to rate the quality of induction and recovery from anesthesia in horses that received traditional GGE (GGE), the ready for use solution (RTU) or Triple Drip (TD), intravenously.

Score	Criteria
Anesthesia induction	
(1) Good	smooth decubitus without head or limb movements
(2) Regular	One or two steps ahead of decubitus without limb movement
(3) Bad	Ataxia before recumbency, limb movements, risk to the animal or staff
Anesthesia recovery	
(1) Good	Rises after 1-3 attempts without ataxia
(2) Regular	Multiple attempts, mild, short-lived ataxia
(3) Bad	Multiple attempts, severe ataxia

The respiratory rate (RR) was lower at T5 and T60 compared to T0 for TD group. The parameter Sp_{O2} was lower at T30 compared with Trec in the RTU group. Heart rate (HR) decreased over time in the TD group, whereas GGE group had higher values compared to RTU and TD groups at times Trec and T10. On the other hand, at times T20, T30 and T40 HRs were higher in GGE group, compared with TD only. In RTU group, MBP increased at T5, compared to T0 ($p<0.001$). In RTU group, mean blood pressure decreased after decubitus at times T10 and T20 ($p<0.001$). RR decreased in group RTU, at T30, and group TD at T40, T50 and T60, compared to T0 ($p<0.009$ and 0.001, respectively) (Table 2).

DISCUSSION

The intravenous 10% GGE-RTU solution induced decubitus quickly and safely in horses, without causing undesirable effects as reported by other authors who used RTU solutions manufactured and marketed outside Brazil (GRANDY & MCDONELL, 1980; MUIR 2009; HALL et al. 2001).

Although the risk of thrombophlebitis and hemolysis using 10% GGE solutions or more (GRANDY & MCDONELL, 1980) has been reported, in this study neither hemolysis was observed in *in vitro* tests nor clinical signs of hemolysis or lesions vascular in any animal. However, this solution is not recommended for patients with established thrombophlebitis or predisposition to the development of vascular changes (HERSCHL et al., 1992).

After rapid administration of the solution prepared before use, one horse from GGE group showed marked ataxia, but no recumbency. Although GGE is successfully used in the field to induce decubitus after using a tranquilizer or sedative, occasionally this may not happen. Plasma concentration of 313 ± 108 mg/mL is required to induce recumbency in horses, and sometimes is achieved by administering doses of 134 ± 34 mg/kg (HUBELL et al. 1980), which are slightly above those used in this study (100 mg/kg). The longer solution administration time for RTU group compared to GGE group can be explained by the rigid material bottle (polyethylene glycol) used to dispense the solution that inhibited manual pressurization during infusion. Using a nontoxic plastic bag should be more convenient and require less infusion time, which is desirable since GGE administration should be done quickly when recumbency is desired or when used as an adjuvant in the induction of anesthesia with ketamine, propofol or sodium thiopental (STAFFIERI & DRIESSEN, 2007). However, it is worth noting that the longer administration time observed in RTU group did not result in failed decubitus induction, shorter decubitus or full recovery times.

Recovery from anesthesia for horses from GGE and RTU groups was classified as excellent, because all horses stood on the first try, with no signs of ataxia or muscle weakness. These findings are consistent with Matthews et al. (1997) who reported quiet and uneventful recoveries in horses after 36 ± 12 minutes, and donkeys, after 32 ± 12 minutes.

Table 1 - Means and standard deviations for weight (kg) and the time between premedication (PAM) and induction (minutes), time of administration (minutes), latency period (seconds), time until sternal recumbency (minutes) and time to standing position (minutes) in horses that received traditional GGE (GGE), the ready for use solution (RTU) or Triple Drip (TD), intravenously.

Groups	weight	Time between PAM and induction	Time of administration	Latency period	Time until sternal decubitus	Time until standing position
EGG	368.5	10.8	2.0	53	23.0	33.0
	[19.12]	[3.3]	[0.0]	[2]	[9.6]	[2.6]
RTU	383.5	10.0	3.5*	150	35.0	38.3
	[31.5]	[2.2]	[1.0]	[36]	[1.4]	[2.6]
TD	362.0	9.5	-	58	35.0	55.3*
	[21.7]	[1.0]	-	[1]	[6.3]	[13.8]

*Significantly different compared to GGE group.

Table 2: Means and standard deviations of respiratory rate (RR), oxyhemoglobin saturation (Sp_{O2}), heart rate (HR), mean blood pressure (MBP), rectal temperature (RT), from time T0 to T60, in horses that received the traditional GGE (GGE), ready for use solution (RTU) or Triple Drip (TD), intravenously.

Parameters	Groups	T0	T5	Trec	T10	T20	T30	T40	T50	T60
RR	**EGG**	20.0	17.0	16.0	14.0	14.0	13.0	-	-	-
		[10.0]	[8.0]	[2.0]	[2.0]	[2.0]	[1.0]	-	-	-
	RTU	20.0	12.0	18.0	17.0	15.0	16.0	-	-	-
		[6.0]	[3.0]	[12.0]	[5.0]	[4.0]	[4.0]	-	-	-
	TD	20.0	10.0#	15.0	14.0	13.0	13.0	14.0	12.0	10.0#
		[13.0]	[2.0]	[9.0]	[7.0]	[6.0]	[6.0]	[10.0]	[6.0]	[5.0]
Sp_{O2}	**EGG**	-	-	96.5	95.3	95.5	96.3	-	-	-
		-	-	[1.9]	[2.5]	[1.9]	[2.8]	-	-	-
	RTU	-	-	96.5	92.3	93.3	91.3#	-	-	-
		-	-	[1.7]	[3.3]	[2.5]	[3.1]	-	-	-
	TD	-	-	98.0	96.7	97.0	96.7	95.0	95.0	95.0
		-	-	[1.0]	[0.6]	[1.0]	[0.6]	[3.4]	[2.2]	[2.2]
HR	**EGG**	39.0	36.0	45.0	46.0	42.0	41.0	-	-	-
		[4.0]	[6.0]	[3.0]	[3.0]	[4.0]	[3.0]	-	-	-
	RTU	40.0	36.0	39.0*	38.0*	36.0	36.0	-	-	-
		[8.0]	[6.0]	[1.0]	[3.0]	[3.0]	[2.0]	-	-	-
	TD	41.0	35.0#	33.0#*	32.0#*	32.0#*	30.0#*	32.0#*	32.0#	32.0#
		[3.0]	[2.0]	[3.0]	[2.0]	[3.0]	[4.0]	[2.0]	[2.0]	[2.0]
MBP	**EGG**	122.8	135.0	105.0	102.0	109.0	107.5	-	-	-
		[12.0]	[26.5]	[38.9]	[24.4]	[20.7]	[17.9]	-	-	-
	RTU	116.5	132.0#	102.5	98.8#	100.0#	102.0	-	-	-
		[11.4]	[9.9]	[7.9]	[5.0]	[8.6]	[9.9]	-	-	-
	TD	117.0	126.0	96.8	105.0	99.5	101.5	100.0	98.5	97.0
		[11.6]	[16.1]	[4.7]	[5.8]	[3.4]	[3.0]	[2.8]	[5.3]	[7.0]
RT	**EGG**	37.1	37.6	37.5	37.4	37.5	37.5	-	-	-
		[1.5]	[1.1]	[1.1]	[1.3]	[1.0]	[0.8]	-	-	-
	RTU	37.6	37.5	37.5	37.4	37.3	37.1#	-	-	-
		[0.5]	[0.6]	[0.7]	[0.5]	[0.7]	[0.5]	-	-	-
	TD	37.5	37.4	37.5	37.4	37.3	37.1	37.0#	36.9#	36.8#
		[0.7]	[0.6]	[0.6]	[0.7]	[0.6]	[0.5]	[0.6]	[0.6]	[0.4]

*Significantly different from GGE. #Significantly different from the value at T0.

On the other hand, the horses from TD group had multiple attempts; longer times elapsed until the standing position and mild ataxia observed were probably due to xylazine, ketamine and midazolam association. In addition to sedation effect, xylazine also relaxes the muscles, which along with GGE can lead to longer recovery times and ataxia (TAYLOR et al., 1992; LUNA et al., 1996). Ketamine administration during anesthesia induction is perhaps the most popular technique used in horses; it induces decubitus in 1 to 3 minutes and, when associated with benzodiazepine, facilitates tracheal intubation due to increased myorelaxation. However, neither ketamine nor GGE have a pharmacokinetic profile ideal for maintaining

anesthesia for prolonged periods (over 90 minutes), which may result in longer recovery due to muscle weakness caused by residual GGE concentrations after continuous infusion (STAFFIERI & DRIESSEN, 2007).

Although all anesthetics may negatively affect cardiorespiratory function, inhaled anesthetics cause greater changes than intravenous anesthetics (LUNA et al., 1996). Therefore, Total Intravenous anesthesia has gained ground over the last several years. The combination of alpha-2 adrenergic agonists with ketamine and GGE usually causes minimal respiratory depression during the first hour, but during procedures lasting longer than 45 minutes the animals should be intubated and receive supplemental oxygen (HALL et al. 2001). This limits the use of this technique in long procedures, since prolonged recumbency associated with respiratory and cardiovascular depression enhances the risk of hypoxemia (STAFFIERI & DRIESSEN, 2007), which may explain the gradual decrease of heart rate and Sp_{O2} in horses from TD group. Moreover, the association with benzodiazepines could enhance muscle relaxation and facilitate intubation but can also increase the depth of anesthesia and potentiate respiratory depression (STAFFIERI & DRIESSEN, 2007).

Although the RR changes observed in this study are similar to those reported by other authors (MUIR et al., 1978; THURMON et al., 1986; YOUNG et al., 1993), Sp_{O2} decrease was more pronounced in RTU group, reaching values compatible with moderate hypoxemia. It is difficult to formulate a plausible explanation for this phenomenon, but due to the small number of animals, the possible interference of vehicle components, propylene glycol and benzyl alcohol could be thought of.

Propylene glycol is used as a vehicle for drugs such as lorazepam, diazepam, etomidate, phenytoin, nitroglycerin, hydralazine, esmolol, phenobarbital, chlordiazepoxide and trimethoprim-sulfamethoxazole (AL-KHAFAJI et al. 2002). There are reports of toxicity after infusion of lorazepam, etomidate, and diazepam and nitroglycerin; manifestations of propylene glycol toxicity include CNS depression, convulsions, cardiac arrhythmias, respiratory and renal failure, and hemolysis (ARBOUR; ESPARIS, 2000). In another study, Al-Khudhairi et al. (1982) did not observe depression of the upper respiratory centers, or changes in the timing of the respiratory cycle, in dogs receiving propylene glycol intravenously in quantities corresponding to 20 mg/kg of diazepam.

On the other hand, benzyl alcohol is an aromatic alcohol used as antimicrobial preservative in various commercial solutions. In the 80's some researchers linked medications containing benzyl alcohol to severe metabolic acidosis, encephalopathy, respiratory depression and death in patients of neonatal units (SILVA et al., 2008). However, the effects of fast or slow infusions of this compound were evaluated in adult animals of various species without finding evidence of toxicity (KIMURA et al., 1971). Benzyl alcohol is oxidized to benzoic acid, conjugated with glycine in the liver and excreted as hippuric acid. This metabolic pathway may not be functional in neonates, leading to accumulation of benzoic acid and benzyl alcohol itself, culminating in toxic effects such as respiratory failure, vasodilation, hypotension, convulsions and paralysis (COMMITTEE ON FETUS AND NEWBORN COMMITTEE ON DRUGS, 1983).

Based on this evidence, there is apparently no reason to link hypoxemia to other components of the formulation. Still, one must consider that the same active ingredient was also used combined with xylazine and ketamine in horses from TD group, without observing the same trend. Further studies should be pursued with a larger number of animals, where hemodynamic and blood gas analysis should be performed to confirm or discard greater incidence of hypoxemia when using RTU solution.

The increase of MBP at T5 was expected, since the agonists of alpha-2 adrenergic receptors cause vasoconstriction and increased peripheral vascular resistance (SINGH et al. 1997). Likewise, the slight decreasing MBP was expected after administration of the solutions, because, although blood pressure may decrease, the cardiac contractility is not affected, so guaiacol glyceryl ether (GGE) does not induce significant hypotension when administered at recommended doses (HUBELL et al. 1980). In fact, at no times MBP values dropped below 55-65 mmHg, which is considered as hypotension in horses (BIDWELL et al., 2007), or below 70 mmHg, the reported limit for horses under inhalation anesthesia with halothane at the risk of complications such as post-anesthetic myopathy (DUKE et al., 2006).

CONCLUSION

The clinical efficacy and safety of 10% GGE-RTU injectable solution for the induction of decubitus and chemical restraint in horses has been demonstrated in this work. Additionally, we also report the compatibility of the GGE-RTU with xylazine and ketamine and safety of this solution to induce anesthesia, with minimal cardiorespiratory changes that do not differ from those reported for conventional GGE solutions prepared before use and associated with these two drugs.

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