Effects of Detomidine Constant Rate Infusion on Blood Glucose and Lactate in Sevoflurane Anesthetized Horses

Priscila Beatriz da Silva Serpa[1,2], Cláudio Corrêa Natalini[1,2,3], Ruben Lundgren Cavalcanti[1,2], José Pedro Nogueira Estrella[2], Bruna Faveiro Pellin de Molnar[1], Daniele Pankowski Bezerra[2,4], Ananda da Rocha Pires[2,4] & Viviane Conde Fernandes[4]

ABSTRACT

Background: The drugs that promote sedation, analgesia, and anesthesia, as inhalatory agents, phenothiazines, benzodiazepines, alpha-2 adrenergic agonists, and opioids, can promote different kinds of side effects. The concept of a balanced anesthesia in equine was developed in order to minimize adverse effects inherent to anesthesia, creating a combination of lower doses of these drugs in comparison with the doses of each one used alone. Alpha-2-adrenoceptor agonists such as xylazine, detomidine, and others, are drugs used for standing sedation, analgesia, and reduction of volatile anesthetic requirement in the equine as well as an agent used to maintenance of arterial blood pressure during anesthesia. Alpha-2 agonists works stimulating receptors of autonomic neurons inducing reduction of heart rate, cardiac output and vascular resistance, hypertension, behavioral changes, and inhibition of insulin secretion. This reduction in insulin levels increases blood glucose concentration in horses due to its lower utilization in insulin-dependent tissues, as muscular and adipose tissues. Muscular tissue is capable to maintain a constant lactate production even in a well oxygenated environment in order to maintain its cellular activity, especially in cases when glucose is not available. To evaluate the effect on blood glucose and lactate, horses were submitted to one hour of detomidine constant rate infusion during sevoflurane inhalatory anesthesia with controlled ventilation, in order to assess blood concentration of glucose and lactate

Materials, Methods & Results: Four adult horses were studied. Detomidine 20 µg.kg^{-1} was used as premedication followed by an association of ketamine and diazepam intravenously as anesthetic induction. After intubation, sevoflurane was vaporized at approximately 2.3 V%. Mechanical ventilation was established. After stabilization, an intravenous continuous rate infusion (CRI) of detomidine 5 µg.kg.h^{-1} was started. Venous blood samples were collected before premedication, prior to detomidine continuous infusion, 20, 40, and 60 min after beginning of infusion, in order to determination of glucose and lactate serum concentrations. After 60 min of detomidine infusion, the horses were allowed to recovery. There was statistical significant hyperglycemia in the horses under CRI of detomidine. There was no significant increase in blood lactate, despite of the hyperlactatemia in some animals.

Discussion: Detomidine CRI of 5 µg.kg.h^{-1} does increase blood glucose levels over normal values but not to levels that could be toxic to tissues, mainly CNS. With low levels of serum insulin, body tissues, mainly muscular and adipose tissues, are unable to capture this available blood glucose and these cells depend on lactate metabolism. The lactate serum concentrations below normal range observed in studied horses suggest that all lactate produced by the tissues is being utilized in the energetic metabolism. In according to many authors, lactate is produced and utilized for mitochondrias as energetic source even in fully oxygenated tissues, which seems to be what happened in this experiment. The present study helps to understand energetic metabolism in horses under general inhaled anesthesia with detomidine CRI, a selective alpha-2-adrenoceptor agonist. In order to better evaluate energetic metabolism during inhaled anesthesia under detomidine influence, other studies are suggested, as prolonged anesthesia duration to evaluate a longer adrenergic stimulus induced by detomidine. Besides, other investigations with detomidine CRI in horses submitted to surgical procedures could provide different responses in energetic metabolism.

Keywords: alpha-2 agonist, energetic metabolism, equine, inhalatory anesthesia.

INTRODUCTION

Equine anesthesia involves control of administration of multiple drugs that can lead to a series of deleterious cardiovascular and respiratory effects. In order to produce sedation, analgesia, anesthesia, and minimize adverse effects of these drugs, the concept of balanced anesthesia was developed [37]. All inhalant anesthetics can induce different levels of dose-dependent cardiovascular depression [28]. Studies showed that drugs like lidocaine [10,18, 25], ketamine (21,38], and alpha-2-adrenoceptor agonists [25,29,30,34,35] can decrease MAC (minimum alveolar concentration) of different inhalant agents and its side effects.

Alpha-2-adrenoceptor agonists such as xylazine, detomidine, and others, are drugs used for standing sedation, analgesia, and reduction of volatile anesthetic requirement in the equine [7]. Alpha-2 agonists works stimulating receptors in peripheral and central nervous system, located pre- and postsynaptically [23] inducing hypertension, bradycardia, atrioventricular block, decreasing cardiac output, and vascular resistance, behavioral changes, and inhibition of insulin secretion [32]. This reduction in insulin levels increases blood glucose concentration in adult horses and ponies [12], and its effect on lactate concentration in plasma is unknown. According to Brooks [2], there is a constant lactate production by oxygenated tissues, especially in muscles, in order to maintain cellular activity.

The objective of this study was to evaluate the effect of detomidine constant rate infusion on blood glucose and lactate in horses submitted to one hour of sevoflurane inhalatory anesthesia with controlled ventilation.

MATERIALS AND METHODS

Four clinically healthy adult mixed breed mares weighing 504.5 kg ± 64.8 were studied. The age varied from 10 to 15 years. Horses were allowed free access to water, and food was withheld 12 h before each anesthesia.

Before premedication, a 14-gauge 5.25 inches catheter was placed in the left jugular vein under local anesthesia with 2% lidocaine. Blood samples were collected prior to each study for baseline glucose and lactate determination. Detomidine[1] 20 μg.kg^{-1} was used as premedication followed by an association of ketamine[2] 2.2 mg.kg^{-1} and diazepam[3] 0.1 mg.kg^{-1} intravenously 15 min after sedation for anesthetic induction. Horses were placed in right lateral recumbency, intubated and connected to an anesthesia machine equipped with a sevoflurane calibrated vaporizer. An initial oxygen flow rate of 20 mL.kg.min^{-1} was instituted until anesthetic stabilization was achieved, followed by 10 mL.kg.min^{-1} in the remaining study time. Sevoflurane[4] was vaporized at a value equivalent to approximately one MAC (minimum alveolar concentration) during all study, which corresponds in the equine species to 2.3 V%. Horses were allowed to breathe spontaneously for 10 min followed by mechanical ventilation. After stabilization, a continuous intravenous infusion of detomidine 5 μg.kg^{-1}.h^{-1} was started. Venous blood samples were collected before premedication (PRE), after stabilization prior to detomidine continuous infusion (T0), 20 min after beginning of infusion (T20), 40 min after beginning of infusion (T40), and 60 min after beginning of infusion (T60), in order to determination of glucose and lactate. After 60 min of detomidine infusion, the horses were allowed to recovery.

One way repeated measure analysis of variance (ANOVA) was used with a significance level of 0.05, and Tukey's test, as a post hoc, was used to isolate group or groups that differ from the others ($P < 0.05$).

RESULTS

Marked hyperglycemia was detected (Table 1) in all horses after detomidine application, considering values of reference established by Kaneko _et al_. [16] that range from 75 to 115 mg/dL. There was statistical significance ($P < 0.05$) in this increase of glucose comparing T0, T20, T40, and T60 with the PRE moment of blood collection.

Considering the means of all horses in each moment of blood collection, there was an increasing concentration of lactate from PRE to T20, followed by its decreasing until T60. Values of reference were considered between 1.11 and 1.78 mmol/L [16]. In moment PRE and T60, one of four horses had hyperlactatemia. In T0 and T40, two horses had high levels of lactate. Horse 1 was the only which had hyperlactatemia before detomidine influence and it decreased serum lactate levels until the end of anesthesia up to a hypolactatemic level. Horses 2 and 3 both followed the same pattern, with lactate within normal ranges, increasing in the first collections and decreasing in the last collections during anesthesia. Horse 4 had high

lactate concentration since the beginning until the end. There were no significant differences in lactate serum concentrations (Table 2) comparing T0, T20, T40, and

T60 with the PRE moment of blood collection, despite of the presence of hyperlactatemia in some horses in some times.

Table 1. Values of blood glucose (mg/dL) from each horse submitted to CRI detomidine during a sevoflurane inhaled anesthesia. Data were collected before premedication (PRE), immediately before infusion (T0), 20 min after beginning of infusion (T20) , 40 min (T40), and 60 min after (T60), when CRI detomidine was discontinued. Values are presented below with means and standard deviations (SD).

	PRE	T0	T20	T40	T60
horse 1	84	190	183	197	211
horse 2	83	214	217	222	224
horse 3	100	198	216	232	240
horse 4	87	187	203	227	237
Mean	88.50	197.25	204.75	219.50	228.00
SD	7.85	12.09	15.84	15.55	13.29

Table 2. Values of blood lactate (mmol/L) from each horse submitted to CRI detomidine during a sevoflurane inhaled anesthesia. Data were collected before premedication (PRE), immediately before infusion (T0), 20 min after beginning of infusion (T20) , 40 min (T40), and 60 min after (T60), when CRI detomidine was discontinued. Values are presented below with means and standard deviations (SD).

	PRE	T0	T20	T40	T60
horse 1	1.92	1.22	1.03	0.99	0.92
horse 2	1.35	0.61	2.00	1.73	1.45
horse 3	0.61	2.23	2.18	1.84	1.62
horse 4	1.44	2.56	2.07	2.29	2.19
Mean	1.33	1.66	1.82	1.71	1.55
SD	0.54	0.90	0.53	0.54	0.52

DISCUSSION

Detomidine is an alpha-2-adrenoceptor agonist 50 times more potent than xylazine [5], and it has also more specificity for its receptors [33]. It has been widely used as a sedative and analgesic agent in equine practice [11]. After intravenous injection, detomidine and its metabolites, 3-hydroxy-detomidine and detomidine 3-carboxylic acid, are first detected by liquid chromatography-mass spectrometry within 0.5, 2 and 15 min respectively, and last detected up to 4, 1.5 and 12 h respectively. Its elimination half life declined approximately in 30 min, demonstrating detomidine high lipophilic behavior with an elevated volume of distribution [14]. Due to its characteristics, a continuous rate infusion of detomidine would be necessary to submit horses to appropriate plasma levels of the drug during general anesthesia as proposed in this study.

The activation of alpha-2-adrenoceptors causes an inhibition of neurotransmission by activation of potassium channels in postsynaptic level [36], and inhibition of calcium channels in presynaptic level [1].

It is mediated by a protein G coupled system which inhibits adenylate cyclase decreasing intracellular cAMP [9]. Through its binding in pancreatic cells, alpha-2-adrenergic agonists markedly decrease insulin secretion, and it causes a hyperglycemia in adult horses [31], but not in foals [26]. As seen in other species, but not proven in horses, this hyperglycemia is accompanied by a hyperglucagonemia [17,20,22,27], which also stimulates glucose release from hepatic glycogen [16].

Hyperglycemia during surgical and anesthetic procedures can be caused by excess of glucose solutions, catecholamine-induced responses to trauma, pain, and sepsis, β-adrenergic blockers, glucocorticosteroids, and systemic diseases, as diabetes mellitus, Cushing's syndrome, pancreatitis, and others conditions [8]. It can induce hypovolemia by osmotic diuresis, dehydratation, electrolytes disturbances, and may increase incidence of cerebral injury when it occurs before an ischemic or hypoxemic event [6]. According to Thurmon *et al.* [31], blood glucose above 600 mg/dL, which can be seen in colic and intestinal

resection surgeries, can cause central nervous system damage and blindness in horses. In this study, glucose values did not surpass 240 mg/dL, although any animal had suffered any nociceptive stimulus or surgical procedure. Perhaps, under a longer detomidine influence or others α_2 agonists, glucose may reach higher and deleterious levels.

With low levels of serum insulin, body tissues, mainly muscular and adipose tissues, are unable to capture this available blood glucose and these cells depend on lactate metabolism [15]. Many authors agree about the new concept of lactate playing a role in maintenance of energetic metabolism during aerobic cellular activity and not just as a waste end product on anoxia or hypoxia situations [3,13]. New theories indicate that lactate is produced and utilized for mitochondrias as energetic source even in fully oxygenated tissues [4,24]. According to this same author, there is a "cell-to-cell" lactate shuttle in the organism, which indicates that lactate produced by one cell can be utilized by another cell and there is an amount of lactate that goes through the interstitium and blood flow, providing a carbon source for oxidation and ATP production in other cells.

In this study, considering that some animals had presented high concentrations of lactate, there was no statistical difference in this increase. The normolactatemia observed could be explained by a serum dilution caused by the fluid regimen applied. The fluid dosage which the four horses were submitted ranged around 10 mL/kg per hour. It could be considered high by Magdesian [19], whom indicates 2-4 mL/kg per hour as basal maintenance infusion. By other hand, all lactate produced to supply energetic needs could be maintaining tissue consumption, do not evidencing any increased serum levels. Longer periods of hyperglycemia could lead to higher values of serum lactate.

Although α_2 agonists decrease respiratory rate, resulting in slightly increased in $PaCO_2$ and mild reductions in PaO_2 [7], horses were mechanical ventilated in this study in order to minimize this effects. Despite these hemodynamic changes, gross clinical signs of inadequate tissue perfusion have not been reported in the animals studied.

CONCLUSION

A continuous rate infusion of detomidine in a dosage of 5 µg.kg.h^{-1} is adequate to maintain horses in a sevoflurane anesthesia, with no clinical evidence of deleterious effects, remaining stabilized, and presenting good recovery. There is a significant but not exacerbated hyperglycemia in horses submitted to alpha 2 agonists, confirmed by this study, with mean serum concentration of lactate within normal reference values for this specie.

SOURCES AND MANUFACTURERS

[1]Dormium V®,Agener União Saúde Animal, Embu-Guaçu, SP, Brazil.

[2]Ketamina®, Agener União Saúde Animal, Embu-Guaçu, SP, Brazil.

[3]Compaz®, Cristália Produtos Químicos e Farmacêuticos Ltda., Itapira, SP, Brazil.

[4]Sevoflurano, Instituto BioChimico Indústria Farmacêutica Ltda., Itatiaia, RJ, Brazil.

REFERENCES

1 **Bean B.P. 1989.** Neurotransmitter inhibition of neuronal calcium currents by changes in channel voltage dependence. *Nature.* 340: 153-156.

2 **Brooks G.A. 2000.** Intra- and extra-cellular lactate shuttles. *Medicine & Science in Sports & Exercise.* 32 4): 790-799.

3 **Brooks G.A. 2002.** Lactate shuttle - between but not within cells? *Journal of Physiology*. 541(2): 333.

4 **Brooks G.A. 2002.** Lactate shuttles in nature. *Biochemical Society Transactions.* 30(2): 258-264.

5 **Chui Y.C., Mutlib A., Esaw B., Zarate R. & Young L.M. 1992.** Detection of detomidine and its metabolites in equine plasma and urine by LC/MS/MS. In: *Proceedings of the 9th International Conference of Racing Analysts and Veterinarians* (New Orleans, EUA). pp.85-92.

6 **Cook D.R. 2006.** Hypoglycemia and hyperglycemia. In: Atlee J.L (Ed). *Complications in anesthesia.* 2nd edn. London: Saunders, pp.657-658.

7 **Daunt D.A. & Steffey E.P. 2002.** Alpha-2 adrenergic agonists as analgesics in horses. *Veterinary Clinics of North America: Equine Practice.* 18(1): 39-46.

8 **De Ruyter M.L. & Harrison B.A. 2006.** Hyperglycemia and diabetic ketoacidosis. In: Atlee J.L (Ed). *Complications in anesthesia.* 2nd edn. London: Saunders, pp.415-418.

9 **Doze V.A., Chen B.X., Tinklenberg J.A., Segal I.S. & Maze M. 1990.** Pertussis toxin and 4-aminopyridine differentially affect the hypnotic-anesthetic action of dexmedetomidine and pentobarbital. *Anesthesiology.* 73(2): 304-307.

10 **Dzikiti T.B., Hellebrekers L.J. & Dijk P. 2003.** Effects of intravenous lidocaine on isoflurane concentration, physiological parameters, metabolic parameters and stress- related hormones in horses undergoing surgery. *Journal of Veterinary Medicine Series A.* 50(4): 190-195.

11 **England G.C.W. & Clarke K.W. 1996.** Alpha-2 adrenoceptor agonists in the horse-a review. *British Veterinary Journal.* 152(6): 641-657.

12 **Gasthuys F., Terpstra P., Van den Hende C. & De Moor A. 1987.** Hyperglycaemia and diuresis during sedation with detomidine in the horse. *Journal of Veterinary Medicine Series A.* 34(1-10): 641-648.

13 **Gladden L.B. 2004.** Lactate metabolism: a new paradigm for the third millennium. *The Journal of Physiology.* 558(1): 5-30.

14 **Grimsrud K.N., Mama K.R., Thomasy S.M. & Stanley S.D. 2009.** Pharmacokinetics of detomidine and its metabolites following intravenous and intramuscular administration in horses. Equine Veterinary Journal. 41(4): 361-365.

15 **Gutsche J. & Deutschman C.S. 2006.** Sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome. In: Atlee J.L (Ed) *Complications in anesthesia.* 2nd edn. London: Saunders, pp. 496-499.

16 **Kaneko J.J., Harvey J.W., & Bruss M.L. 2008.** Clinical biochemistry of domestic animals. 6th edn. San Diego: Elsevier Academic Press, pp.884-885.

17 **Knudtzon J. 1984.** Adrenergic effects on plasma levels of glucagon, insulin, glucose and free fatty acids in rabbits. *Hormone and Metabolic Research.* 16(8): 415-422.

18 **Kruger K. & Stegmann G.F. 2009.** Partial intravenous anaesthesia in 5 horses using ketamine, lidocaine, medetomidine and halothane. *Journal of South African Veteriary Associations.* 80(4): 233-236.

19 **Magdesian K.G. 2004.** Monitoring the critically ill equine patient. *Veterinary Clinics of North America: Equine Practice.* 20(1): 11-39.

20 **Muggaberg J. & Brockman R.P. 1982.** Effect of adrenergic drugs on glucose and plasma glucagon and insulin responses to xylazine in sheep. *Research in Veterinary Science.* 33 1): 118-120.

21 **Muir III W.W. & Sams R. 1992.** Effects of ketamine infusion on halothane minimal alveolar concentration in horses. *American Journal of Veterinary Research.* 53(10): 1802-1806.

22 **Oda S., Fujimura K., Sasaki Y. & Ohneda A. 1991.** α2-adrenergic modulation of glucagon and insulin secretions in sheep. *The Tohoku Journal of Experimental Medicine.* 163(2): 101-110.

23 **Pertovaara A. 1993.** Antinociception induced by alpha-2-adrenoceptor agonists, with special emphasis on medetomidine studies. *Progress in Neurobiology.* 40(6): 691-709.

24 **Philp A., Macdonald A.L. & Watt P.W. 2005.** Lactate - a signal coordinating cell and systemic function. *The Journal of Experimental Biology.* 208(24): 4561-4575.

25 **Ringer S.K., Kalchofner K., Boller J., Fürst A. & Bettschart-Wolfensberger R. 2007.** A clinical comparison of two anaesthetic protocols using lidocaine or medetomidine in horses. *Veterinary Anaesthesia and Analgesia.* 34(4): 257-268.

26 **Robertson S.A., Carter S.W., Donovan M. & Steele C. 1990.** Effects of intravenous xylazine hydrochloride on blood glucose, plasma insulin and rectal temperature in neonatal foals. *Equine Veterinary Journal.* 22(1): 43-47.

27 **Samols E. & Weir G.C. 1979.** Adrenergic modulation of pancreatic A, B, and D cells –α-adrenergic suppression and β-adrenergic stimulation of somatostatin secretion, α-adrenergic stimulation of glucagon secretion in the perfused dog pancreas. *The Journal of Clinical Investigation.* 63(2): 230-238.

28 **Steffey E.P. & Howland D. 1978.** Cardiovascular effects of halothane in the horse. *American Journal of Veterinary Research.* 39(4): 611-615.

29 **Steffey E.P. & Pascoe P.J. 1991.** Xylazine reduces the isoflurane MAC in horses. *Veterinary Surgery.* 20(2): 158.

30 **Steffey E.P., Pascoe P.J., Woliner M.J. & Berryman E.R. 2000.** Effects of xylazine hydrochloride during isoflurane-induced anesthesia in horses. *American Journal of Veterinary Research.* 61(10): 1225-1231.

31 Thurmon J.C., Davis C.N., Davis L.E., Stoker R.A., Benson G.J. & Lock T.F. 1982. Xylazine hydrochloride-induced hyperglycemia and hypoinsulinemia in thoroughbred horses. *Journal of Veterinary Pharmacology Therapy.* 5(4): 241-245.

32 Valverde A. 2010. Alpha-2 agonists as pain therapy in horses. V*eterinary Clinics of North America: Equine Practice.* 26(3): 515-532.

33 Virtanen R. & MacDonald E. 1985. Comparison of the effects of detomidine and xylazien on some adrenoceptor-mediated responses in the central and peripheral nervous systems. *European Journal of Pharmacology.* 115(2-3): 277-284.

34 Wagner A.E., Dunlop C.I., Heath R.B., Turner A.S. & Trotter G.W. 1992. Hemodynamic function during neurectomy in halothane anesthetized horses with or without constant dose detomidine infusion. *Veterinary Surgery.* 21(3): 248-255.

35 Wagner A.E., Muir III W.W. & Hinchcliff K.W. 1991. Cardiovascular effects of xylazine and detomidine in horses. *American Journal of Veterinary Research.* 52(5): 651-657.

36 Williams J.T., Henderson G. & North R.A. 1985. Characterization of alpha-2-adrenoceptors which increase potassium conductance in rat locus coeruleus neurons. *Neuroscience.* 14(1): 95-101.

37 Wolfensberger R.B. & Larenza M.P. 2007. Balanced anesthesia in the equine. *Clinical Techniques of Equine Practice.* 6(2): 104-110.

38 Yamashita K., Muir III W.W., Tsubakishita S., Abrahamsen E., Lerch P., Izumisawa Y. & Kotani T. 2002. Infusion of guaifenesin, ketamine, and medetomidine in combination with inhalation of sevoflurane versus inhalation of sevoflurane alone for anesthesia of horses. *Journal of American Veterinary Medical Association.* 221(8): 1150-1155.