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ELECTROENCEPHALOGRAPHIC AND ELECTROMYOGRAPHIC CHANGES DURING THE USE OF DETOMIDINE AND DETOMIDINE-BUTORPHANOL COMBINATION IN STANDING HORSES

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Clinically, the use of detomidine and butorphanol is suitable for sedation and deepening of analgosedation. The aim of our study was to establish the influence of detomidine used alone and a butorphanol-detomidine combination on brain activity and to evaluate and compare brain responses (using electroencephalography, EEG) by recording SEF_{90} (spectral edge frequency 90%), individual brain wave fractions (beta, alpha, theta and delta) and electromyographic (EMG) changes in the left temporal muscle in standing horses. Ten clinically healthy cold-blooded horses were divided into two groups of five animals each. Group I received detomidine and Group II received detomidine followed by butorphanol 10 min later. SEF_{90}, individual brain wave fractions and EMG were recorded with a pEEG (processed EEG) monitor using computerised processed electroencephalography and electromyography. The present study found that detomidine alone and the detomidine-butorphanol combination significantly reduced SEF_{90} and EMG, and they caused changes in individual brain wave fractions during sedation and particularly during analgosedation. The EMG results showed that the detomidine-butorphanol combination provided greater and longer muscle relaxation. Our EEG and EMG results confirmed that the detomidine-butorphanol combination is safer and more appropriate for painless and non-painless procedures on standing horses compared to detomidine alone.

Key words: EEG, EMG, detomidine, butorphanol, standing horses

During a surgical procedure on a standing horse, sedation and analgosedation are used. Sedation and analgosedation cause insensitivity to pain, tranquillity, muscle relaxation and sleep during the surgery (Munroe and Young, 1991; Muir and Hubbell, 1995; van Dijk et al., 2003). This state is induced by appro-

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priate drugs, i.e. sedatives (e.g. alpha$_2$ agonists) and analgesics (e.g. opioids). Sedation inhibits the function of the central nervous system (CNS), while the patient remains awake but tranquil. Inhibition of the cerebral cortex depends on the type and dose of the sedative used. Analgosedation is a state of hypnosis and analgesia, caused by a combination of sedatives and analgesics (opiates or opioids) (Muir and Hubbell, 1995). It causes changes in the state of consciousness and reduces response to pain. Analgosedation is used in surgeries when general anaesthesia is not necessary (Muir and Hubbell, 1991; Otto and Short, 1991).

The effectiveness of both analgesia and sedation is clinically assessed by a combination of typical signs, manifested by tranquillity and sleep: absence of sensitivity to pain, head lowering, some muscle relaxation, dropped lower lip, reduced heart and breathing rate, together with reluctance to move and ataxia. Many of these changes are a consequence of differences in brain electrical activity, which are reflected in changes of the brain waves (Otto and Short, 1991; Short et al., 1992; Entholzner et al., 1995; Muir and Hubbell, 1995; Itamoto et al., 2001). Brain waves appear in the cerebral cortex in the form of electrical potentials and can be detected by placing electrodes on the skin of the head (Despopoulos and Silbernagl, 1991). The intensity and shape of brain electrical activity are a reflection of brain stimulation, caused by the functioning of the reticular activation system. The potential of brain waves at the surface of the skull is between 0 and 300 microvolts (μV). Their frequencies range from one wave every few milliseconds to 50 or more waves within a second (Hz). The shape of brain waves depends largely on the level of activity of the cerebral cortex. Waves differ significantly between the waking state and sleep. Brain waves are mostly irregular in shape; therefore, there is no general pattern of electroencephalography (EEG). The shape of brain activity or waves is classified as alpha, beta, theta and delta waves (Despopoulos and Silbernagl, 1991; Litscher, 1995).

Detomidine, an alpha-2-adrenergic agonist, and butorphanol are used frequently in equine clinical practice (Clarke and Paton, 1988; Riebold et al., 1995; Wilson et al., 2002; Latimer et al., 2003). Our hypothesis was that the use of detomidine alone and in combination with butorphanol has a powerful influence on brain electroencephalographic and electromyographic activity in standing horses. The aim of our study was to establish the influence of detomidine alone and the butorphanol-detomidine combination on brain activity and to evaluate and compare brain responses (EEG) by recording SEF_{90} (spectral edge frequency 90%), individual brain wave fractions (beta, alpha, theta and delta) and EMG changes on the left temporal muscle in standing horses.

SEF_{90} is a frequency that covers 90% of the capacity of the frequency spectrum and is a sensitive indicator of changes in brain activity (Litscher et al., 1995; Fabregas et al., 2001).

Materials and methods

The study protocol was approved by the Ministry of Agriculture, Forestry and Food, Veterinary Administration of the Republic of Slovenia.

Ten clinically healthy cold-blooded horses (4 geldings, 6 mares; age: 7 ± 0.33 years; body weight: 422.10 ± 18.21 kg) were divided into two groups of five animals each. Group I (n = 5) received detomidine (Domosedan, Orion, Espoo, Finland; 22.0 μg/kg). Group II (n = 5) received detomidine (22.0 μg/kg) followed by butorphanol (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa, USA; 0.05 mg/kg) 10 min later. The EEG monitor used was pEEG monitor (processed EEG, Dräger, Lübeck, Austria, version 3.01) with computerised processed electroencephalography and electromyography, dual channel, bipolar frontal, frequency range 1.5 to 30 Hz, amplitude - potential range 25 to 200 μV, which, by means of five direct current electrodes (Agilent Technologies, Andover, USA; Neonatal/Pediatric Solid Gel ECG Monitoring Snap Electrode, No. 13951C), receives and modifies two EEG signals from the left and right cerebral hemispheres recording SEF_{90}, individual EEG wave fractions in percentage (beta, alpha, theta, delta), and EMG. By means of fast Fourier transformation, the pEEG monitor provides an adequate amplitude (μV) for each frequency of the EEG signal (Hz) every two seconds, as well as the ratios of individual brain wave frequencies that are automatically calculated from the raw (computer unprocessed) EEG data (Dick et al., 1992; Schäfer, 1992). The electrode resistance, which must be between 0 and 40 kΩ, is controlled automatically. Electrodes were attached to the designated shaved places on the head (in the middle of the frontal region on both sides, in the middle of the parietal region on both sides of the head and in the upper third of the interfrontal suture) and were connected to the pEEG monitor. The changes of EEG wave fractions were monitored on the screen. The pEEG monitor was directly linked to a PC. From the left pair of electrodes, the pEEG monitor provides also the EMG activity of the left temporal muscle (electromyography), which indicates its electrical activity and the level of relaxation of this striated muscle. Electrodes for the EEG and EMG are identical. EMG was recorded at the left temporal muscle (Litscher, 1995; Litscher et al., 1995). Recording (1/min) started 5 min before drug administration (–5–0 min) and continued for 60 min, divided into two parts: 1–30 min and 30–60 min. Before and during the study, the analgesic effect of detomidine and butorphanol was evaluated every 5 min using a plastic cylinder with 1 cm² surface that was fixed with a blowing cuff with the manometer on the left metacarpal bone. By blowing the cuff (Tensoplus OSZ 2, Speidel+Keller, Jungingen, Germany), a pressure of 100 mm Hg was reached on the surface of the cylinder and was maintained for 1 min. The horses reacted to the applied pressure stimulus with the movement of the leg only before the administration of the drugs.

The results were subjected to analysis of variance (ANOVA) and correlation analysis using Excel 6.0 software, statistical program ANOVA and correlation test according to Pearson. $P < 0.05$ was considered as significant. Results are given as mean ± SE.

Results

Measurements were divided into three time periods: initial values representing the results measured before the beginning of the experiment and two successive parts (first and second part) representing the values recorded from the 1st to the 30th minute and from the 30th to the 60th minute.

Time: –5 – 0 min

Before the experiment, horses showed no signs of agitation. The body position was the normal standing posture as expected. The head and neck were appropriately raised, without jerky movements or glancing around. The horses did not shift on the spot or swish their tails, which is frequently observed in agitated horses. Administration of pressure on the leg in the same way as during the experiment resulted in horses jerking the leg away. Pressure stimulus in standing animals, without sedatives and analgesics, increased their SEF_{90} and individual brain wave fractions of beta, alpha and theta waves, and reduced delta brain wave fractions.

Table 1

SEF_{90} and EMG (mean ± SE)

		Baseline values (5 min before the study)	First part of the study (from 1st to 30th min)		Second part of the study (from 30th to 60th min)	
			Group I	Group II	Group I	Group II
SEF_{90}	L (Hz)	19.9 ± 1.2	12.8^{**} ± 0.4	11.6^{**} ± 0.6	15.4^{*} ± 07	10.5^{**} ± 0.5^{+}
SEF_{90}	R (Hz)	20.2 ± 1.1	14.1^{**} ± 0.5	12.8^{**} ± 0.6	15.9^{*} ± 0.8	11.7^{**} ± 0.6^{+}
EMG	(μV)	63.0 ± 4.7	16.1^{**} ± 0.7	16.7^{**} ± 1.1	16.6^{*} ± 0.8	11.5^{**} ± 0.8^{+}

Group I: detomidine; Group II: detomidine + butorphanol; L: left brain hemisphere; R: right brain hemisphere; $^{*}P < 0.01$ compared to baseline values; $^{**}P < 0.001$ compared to baseline values; $^{+}P < 0.001$ compared to Group I

The initial values (before drug administration) of SEF_{90} and EMG were the highest during the entire study (Table 1). Also, the proportion of beta brain wave fractions, characterised as being relatively high during the waking state or in the phase of active brain functioning and responding to the environment, was very high. The proportion of alpha brain wave fractions, which together with beta waves represent high-frequency waves, represented a small portion of the

registered waves. A larger proportion was represented by theta wave fractions. The proportion of delta brain wave fractions was the largest among the measured waves (Table 2).

Table 2

EEG – Individual brain wave fractions in % (mean ± SE)

Brain waves	Baseline values (5 min before the study) (%)	First part of the study (from 1st to 30th min) (%)		Second part of the study (from 30th to 60th min) (%)	
		Group I	Group II	Group I	Group II
beta L	21.0 ± 3.2	$12.6^{**} \pm 0.8$	$11.6^{**} \pm 1.3$	18.8 ± 1.4	$9.4^{**} \pm 1.1^{+}$
beta R	24.4 ± 3.0	$18.1^{*} \pm 1.2$	$15.3^{*} \pm 1.8$	23.2 ± 1.8	$11.3^{**} \pm 1.4^{+}$
alpha L	1.4 ± 0.2	$4.4^{**} \pm 0.2$	$4.2^{**} \pm 0.2$	$4.0^{**} \pm 0.3$	$5.0^{**} \pm 0.2^{++}$
alpha R	1.8 ± 0.3	$4.5^{**} \pm 0.2$	$4.2^{**} \pm 0.2$	$4.4^{**} \pm 0.3$	$5.4^{**} \pm 0.2^{++}$
theta L	4.4 ± 0.3	$9.0^{**} \pm 0.3$	$9.7^{**} \pm 0.5$	4.9 ± 0.3	$12.1^{**} \pm 0.6^{+}$
theta R	3.9 ± 0.3	$8.4^{**} \pm 0.3$	$9.3^{**} \pm 0.5$	$5.3^{*} \pm 0.4$	$11.0^{**} \pm 0.5^{+}$
delta L	72.6 ± 3.1	73.3 ± 0.9	73.9 ± 1.4	71.5 ± 1.8	72.9 ± 1.2
delta R	69.4 ± 3.0	68.3 ± 1.2	70.6 ± 1.8	66.5 ± 2.1	$71.7 \pm 1.4^{+++}$

Group I: detomidine; Group II: detomidine + butorphanol; L: left brain hemisphere; R: right brain hemisphere; $^{*}P < 0.01$ compared to baseline values; $^{**}P < 0.001$ compared to baseline values; $^{+}P < 0.001$ compared to Group I; $^{++}P < 0.02$ compared to Group I; $^{+++}P < 0.04$ compared to Group I

Time: 0 – 30 min

In both groups, SEF_{90} values were significantly lower when compared to baseline values. SEF_{90} changes from the baseline did not differ significantly between the two groups. EMG values were significantly lower in comparison to the baseline values in both groups. However, there was no significant difference in the EMG values between the two groups (Table 1).

Compared to the initial values, beta waves were reduced significantly ($P < 0.05$) in both groups. The reduction was higher in Group II compared to Group I. However, the difference was not statistically significant. The proportion of alpha wave fraction was significantly increased ($P < 0.05$) in both groups. The proportion of theta wave fraction was significantly increased ($P < 0.05$) in both groups, with slightly lower values in Group I. There was no difference in the percentage of delta wave fraction in the two groups as compared to baseline levels (Table 2).

No significant difference was observed in the activities of the two cerebral hemispheres.

Time: 30 – 60 min

From the 30th to the 60th minute, SEF_{90} values were significantly lower ($P < 0.05$) in comparison with the baseline values in both groups. Additionally, the difference in changes in SEF_{90} levels between the two groups was also significant ($P < 0.05$). Similarly, EMG values were significantly reduced in both

groups when compared to baseline levels and the observed changes were significantly different ($P < 0.05$) between the two groups (Table 1).

In Group I, the beta brain wave fraction was reduced, but the change did not reach the level of statistical significance. However, the alpha wave fraction increased significantly ($P < 0.05$). The theta wave fraction also increased significantly, although only in the right hemisphere. The reduction of delta wave fraction was insignificant.

In Group II, the beta wave fraction was reduced significantly ($P < 0.05$), while the alpha and theta wave fractions increased significantly ($P < 0.05$). The increase of the delta wave fractions was insignificant.

Comparisons between the two groups showed a significantly ($P < 0.05$) lower proportion of beta wave fraction in Group II. There was no difference between the groups in the proportion of alpha wave fraction. The proportions of theta wave fractions were significantly higher in the second group and the proportions of the delta wave fraction were significantly higher in Group II but only in the right hemisphere.

A comparison of brain wave fractions between Group I (sedation) and Group II (analgosedation) showed negative correlation between beta and delta wave fractions in both cerebral hemispheres.

Discussion

Detomidine, an alpha-2-adrenergic agonist, and butorphanol, an opioid analgesic, are frequently used together in various horse therapies because they function well as sedatives and analgesics. Detomidine administered alone causes changes in the CNS (Gleed, 1987; Muir and Hubbell, 1995) resulting in deep sedation and muscle relaxation, depending on the dose of drug used.

In the present study, deep sedation was induced by detomidine in Group I of horses. Group II was analgosedated by the use of a combination of detomidine and butorphanol. A strong influence of detomidine on the CNS as noted by a significant decrease in the value of SEF_{90} and greater muscle relaxation with a significant decrease in EMG values was observed.

Using spectral analysis, Short et al. (1992) evaluated the effect of cumulative administration of medetomidine, an alpha-2-adrenergic agonist, both alone and in combination with halothane or ketamine in laboratory beagles. In this report, medetomidine significantly reduced cerebral activity, which is comparable to the results of our study.

The study of Itamoto et al. (2001), where the effect of medetomidine (different doses) on the EEG was characterised and quantitative EEG analysis used for evaluating sedation levels in dogs, showed that medetomidine has a similar effect on the EEG to that of detomidine used in our study.

The amount of beta waves decreased in both groups, which is characteristic of animals falling asleep. Similarly, the amount of theta waves increased, which is also typical of sleeping animals. However, the amount of alpha waves increased in both groups. Decreased amount of beta waves and increased amount of alpha and theta waves signify a transition of awake, calm and non-active horses to a sedated state (Guyton, 1981; Despopoulos and Silbernagl, 1991). According to the parameters monitored, the effect of detomidine was not influenced by butorphanol during this period.

The second part represents a state of deep sedation and analgosedation. According to clinical signs, butorphanol has a very strong effect during this period of analgosedation. Therefore, the results from this period are the most relevant. In this part of the study, a change in the effect of the drugs used on the nervous system was observed in both groups.

In Group I, the inhibitory effect of detomidine on the CNS started to decline as demonstrated by a significant increase in SEF_{90} values. In Group II, the combination of detomidine and butorphanol extended the effects on the CNS, as noted by a further decrease of SEF_{90} (Orsini, 1988; Plumb, 1995) together with muscle relaxation, demonstrated by a significant decrease in EMG values.

With the gradual inactivation of detomidine, the pattern of brain waves changed in Group I. The amount of beta waves increased while the amount of theta waves decreased, which is characteristic of waking and active animals. In Group II, the amount of beta waves further decreased while the amount of alpha and theta waves increased. This led to a further inhibition of the CNS and deeper analgosedation.

Despite the changes in beta, alpha and theta waves, the percentage of delta waves did not change significantly throughout the study, although such changes in delta waves most often occur during sedation and sleep (Mysinger, 1985; Entholzner et al., 1995). Considering that the percentage of delta waves in non-active and calm horses did not change during the study, it appears that detomidine and butorphanol do not affect delta waves during sedation and analgosedation.

Based on the measurements of brain parameters (SEF_{90}, individual brain wave fractions together with EMG), the present study found that in standing horses the addition of butorphanol to detomidine induces significantly deeper and longer sedation and analgesia (analgosedation), together with greater muscle relaxation after a certain time interval following the administration of the two drugs.

Our EEG and EMG results confirm that the detomidine-butorphanol combination is safer and more appropriate for painless and non-painless procedures in standing horses than detomidine used alone.

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References

Clarke, K. W. and Paton, B. S. (1988): Combined use of detomidine with opiates in the horse. Equine Vet. J. **20,** 331–334.

Despopoulos, A. and Silbernagl, S. (1991): Colour Atlas of Physiology. 4th edition. Thieme Medical Publishers, New York, USA. pp. 272–293.

Dick, W., Gurman, G., Schäfer, M. and Moecke, H. (1992): Can pEEG monitoring improve the management of general anaesthesia? Dräger, Industrial Forum, Hague, The Netherlands. p. 56.

Entholzner, E., Mielke, L., Pichlmeier, R., Weber, F. and Schneck, H. (1995): EEG Veränderungen unter Sedierung mit g-Hydroxybuttersäure (GHB). Anaesthesist **44,** 345–350.

Fabregas, N., Gambus, P., Troconiz, I., Valero, R., Guix, E. and Zavala, E. (2001): Use of electroencephalographic spectral edge frequency to monitor sedation in chronically ill patients (in Spanish). Rev. Esp. Anestesiol. Reanim. **48,** 314–320.

Guyton, A. C. (1981): Textbook of Medical Physiology. 6th edition. W. B. Saunders, Philadelphia, USA. p. 6.

Gleed, R. D. (1987): Tranquilizers and sedatives. In: Short, C. E. (ed.) Principles and Practice of Veterinary Anesthesia. Williams & Wilkins, Baltimore, USA. pp. 17–27.

Itamoto, K., Taura, Y., Wada, N., Taga, A., Takuma, T., Matsumura, H. and Miyara, T. (2001): Effect of medetomidine on electroencephalography and use of a quantitative electroencephalograph for evaluating sedation levels in dogs. J. Vet. Med. **48,** 525–535.

Latimer, F. G., Eades, S. C., Pettifer, G., Tetens, J., Hosgood, G. and Moore, R. M. (2003): Cardiopulmonary, blood and peritoneal fluid alterations associated with abdominal insufflation of carbon dioxide in standing horses. Equine Vet. J. **35,** 283–290.

Litscher, G. (1995): Cerebral monitoring in anaesthesia and intensive care medicine. Biomed. Tech. **40,** 229–234.

Litscher, G., Schwarz, G. and List, W. F. (1995): EEG Langzeitüberwachung. Der Einsatz des Dräger pEEG-Monitors in der Intensivtherapie. Universitätsklinik für Anästhesiologie, Graz, Austria. p. 31.

Mysinger, P. W. (1985): Electroencephalographic patterns of clinically normal, sedated and tranquillised newborn foals and adult horses. Am. J. Vet. Res. **46,** 36–41.

Muir, W. W. and Hubbell, J. A. E. (1991): Anesthetic techniques. In: Muir, W. W. and Hubbell, J. A. E. (eds) Equine Anesthesia, Monitoring and Emergency Therapy. Mosby, St. Luis, USA. pp. 444–460.

Muir, W. W. and Hubbell, J. A. E. (1995): Handbook of Veterinary Anesthesia. 2nd edition. Mosby, St. Luis, USA. pp. 3–38.

Munroe, G. and Young, L. (1991): Standing chemical restraint in the horse. In Practice **13,** 163–166.

Orsini, J. A. (1988): Butorphanol tartrate: pharmacology and clinical indications. Comp. Cont. Educ. Pract. Vet. **10,** 849–854.

Otto, K. and Short, C. E. (1991): EEG power spectrum analysis as a monitor of anaesthetic depth in horses. Vet. Surg. **20,** 362–371.

Plumb, D. C. (1995): Veterinary Drug Handbook. University Press, Iowa State, USA. pp. 97–99.

Riebold, T. W., Geiser, D. R. and Goble, D. O. (1995): Anaesthetic agents and ancillary drugs. In: Riebold, T. W., Geiser, D. R. and Goble, D. O. (eds) Large Animals Anesthesia. Principles and Techniques. 2nd edition. Iowa State University Press, Ames, USA. pp. 20–33.

Schäfer, M. (1992): A protocol for studying the depth of anaesthesia using the spectral edge frequency. Dräger Industrial Forum, Hague, The Netherlands. pp. 9–15.

Short, C. E., Räihä, J. E., Räihä, M. P. and Otto, K. (1992): Comparison of neurologic responses to the use of medetomidine as a sole agent or preanesthetic in laboratory beagles. Acta Vet. Scand. **33,** 77–88.

Van Dijk, P., Lankveld, D. P., Rijkenhuizen, A. B. and Jonker, F. H. (2003): Hormonal, metabolic and physiological surgery using a detomidine-buprenorphine combination in standing horses. Vet. Anaesth. Analg. **30,** 72–80.

Wilson, D. V., Bohart, G. V., Evans, A. T., Robertson, S. and Rondenay, Y. (2002): Retrospective analysis of detomidine infusion for standing chemical restraint in 51 horses. Vet. Anaesth. Analg. **29,** 54–57.