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Accelerometric Evaluation of the Locomotor Pattern After Administration of Morphine in Conscious Healthy Horses

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ABSTRACT

The objective of the present study was to compare, using accelerometry, the gait changes produced after administration of a dose of 0.2 mg/kg of morphine at the walk in healthy horses. Six mature horses were used, and all animals received two different treatments with, at least, two weeks interval in between. Treatments administered consisted of a single dose of 10 ml of saline solution or a total of 0.2 mg/kg of morphine diluted in 10 ml of saline solution. A three-dimensional accelerometric device was used to collect data continuously while horses were walking. The walking test was performed 10 min prior to injection, and then at 5, 10, 15 and 20 min after injection and then every 10 min for 3 h. Eight variables were calculated including stride kinematic, coordination and energetic parameters. Additionally, the force of acceleration and three components of the power were calculated. Significant interaction was only observed for stride length, propulsion power and the propulsive part of the total power with a reduction in values after morphine administration. Compared to baseline values, stride length values were significantly reduced for 80 min and again 110 min after injection of the opioid and at 5, 15, 20, 30 and 40 min in the case of propulsion power values. For the propulsion component of power, these differences were observed for 20 min when compared to baseline values. The administration of 0.2 mg/kg of morphine to conscious healthy horses produces limited effects on the gait pattern of horses and the effects on locomotor activity are minimal at this dose, not being an important concern for the administration of analgesia in a clinical setting.

1. Introduction

Opiates are potent analgesics widely used in human and small animal practices. In horses, several opiate molecules are available for their analgesic effects but are less commonly used as the analgesic potency of opiates is not readily and consistently quantifiable and also due to undesirable side effects [1]. In the case of morphine, doses of 0.2 mg/kg provide detectable analgesia in horses [2] and in clinical settings, morphine significantly improved the quality of recovery when added to a standard anaesthetic protocol [3]. Additionally, the administration of a constant rate infusion intraoperatively of dexmedetomidine (1.75 μg/kg bwt/h) relative to morphine (0.1 mg/kg bwt/h) to horses produced better recovery scores [4]. Nevertheless, particularly mu (μ) opioid agonists, cause a dose-dependent increase in muscle tone and locomotor activity [1,5] and this unwanted excitant behaviour could have potential deleterious consequences if morphine is used as an analgesic in certain clinical conditions. This effect could be produced after stimulation of the central nervous system resulting in excitement and agitation [6]. For this reason, opioids are frequently combined with sedative drugs, most commonly alpha-2 adrenergic but also phenothiazines [1]. In addition, this combination of drugs also provides analgesia for painful conditions and ideal chemical restraint..

Gait alterations, either in the form of incoordination or because of increases in locomotor activity, are one of the most relevant disadvantages produced after the administration of different sedative and analgesic drugs and these alterations have always been estimated using subjective scales. In the last decade, a more accurate, portable and low cost accelerometric method has been used to quantify gait changes [7]. Accelerometers are kinetic assessment

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techniques that measure acceleration of the surface to which they are attached [8]. They should be firmly attached to the body segment under study [9] and have been widely used, both in human and veterinary medicine, to quantify physical activity and compare normal and diseased gait patterns [10–12]. The effect on the gait pattern of the administration of several analgesic and sedative drugs has been evaluated using accelerometry and inertial sensors [7,13,14] and recently, the effect of some opiates has also been quantified [15,16].

The selection of the most indicated opioid in each clinical scenario is based on the duration of its action and the precise behavioural changes caused by this drug. Therefore, the objective of this current study is to evaluate and compare, using accelerometry, the gait alterations produced after administration of morphine in conscious healthy horses. Our hypothesis is that morphine effects on locomotor activity will be easily quantified using accelerometry and that the administration of 0.2 mg/kg of morphine IV would result in minimal effects on locomotor activity.

2. Materials and methods

2.1. Horses

Six mature horses (four mares, two geldings), with a mean (± SD) age of 13.2 ± 8.3 years (range; 4–2 years) and a mean bodyweight (BW) of 425.8 ± 10.2 kg (range; 418–441 kg) were used. A full clinical examination was performed on all horses to ensure they were healthy and sound. The Complutense University Animal Care and Use Committee and the Committee of the Government of Madrid reviewed and approved the experimental protocol.

2.2. Treatment and experimental protocol

Horses were randomly injected with either a total of 10 ml of saline solution (Solución salina fisiológica al 0.9%, B/BRAUN Medical S.A., Spain) (control treatment) or a total of 0.2 mg/kg of morphine hydrochloride solution (Morfina Braun 20 mg/ml, B/BRAUN Medical S.A., Spain) diluted in saline solution to a volume of 10 mL (morphine treatment). Treatments were administered via an intravenous 16G catheter (Surflo, Terumo Europe N.V., Leuven, Belgium), inserted into the left jugular vein. A minimum of 14 days between each treatment was established with random determination of the order of injections.

The portable gait analyser (Equimetrix, Centaure Metrix, France) included an acceleration sensor (3D +/- 6 g), a data logger and a scientific software program (Equimetrix-Centaure 3D Matlab 5, The MathWorks Inc) for processing of the acceleration signals. The three-dimensional accelerometric device consisted of three orthogonal accelerometers measuring accelerations at the sacrum, along the dorsoventral, longitudinal, and lateral axes of the horse. This recorder collected data continuously while the horse was walking, at a sampling rate of 100 Hz. Positive values were obtained when accelerations were in dorsal, cranial and left directions. The data logger was inserted into a leather pocket fixed on the left side of an elastic girth fastened onto the thorax and transferred to a computer after the tests were finished.

Each horse performed 21 walking trials and each trial involved an accelerometric gait assessment. The horse, with the accelerometer transducer in position, was walked at its own chosen speed and the recording was carried out along a 50 m concrete track covered by a 2 cm thick rubber mat. Only the way down was considered because the way back was always faster due to napping behaviour.

On the day of the study, the three-dimensional accelerometric sensor was attached to the skin over the midline of the sacrum region using double adhesive tape. Ten minutes prior to injection, the horse was walked three times over 50 m and baseline accelerometric recordings were then registered. The horse was then injected and accelerometric recordings were repeated 5, 10, 15 and 20 min after the injection and then every 10 min for 3 h. The walking test was performed three times at the baseline time point (−10 min), once at 5, 10, 15 and 20 min after injection and twice in the remaining recordings (at 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170 and 180 min).

2.3. Data collection

The validation and reproducibility of the accelerometric measurements with the mentioned portable gait analyser (Equimetrix, Centaure Metrix, France) have previously been described [7,17,18]. The following studied kinematic, coordination and energetic variables have also been described [17,19–22].

The kinematic variables included speed (S; m/s), stride frequency (SF; cycles/s or Hz) and stride length (SL; m). The unique coordination variable measured was regularity (REG; dimensionless), determined to assess the acceleration pattern similarity of successive strides over the course of time. The energetic variables included dorsoventral power or activity (DVP; W/kg); propulsive power, craniocaudal or longitudinal activity (PP; W/kg); mediolateral power, lateral or side-to-side activity (MLP; W/kg); and total power (TP; W/kg), defined as the sum of the three powers calculated in each axis. Additionally, the force of acceleration (F; N/kg) was calculated by dividing the TP of acceleration by speed to avoid potential bias due to different speeds. Finally, the mediolateral, dorsoventral and propulsive power as a percentage of TP (%MLP, %DVP and %PP respectively) were calculated by dividing the different power components by the TP.

Each accelerometric variable was calculated at each second, 21 times at different time instants of stabilised walking, starting in the fifth second after the beginning of the test and finishing at 25 seconds. The walking distance was sufficient and periods of non-stabilised walking at the beginning and end of the test were eliminated. The final value for each parameter at each time point was calculated as the mean of the 21 measurements, three times (63 measurements) for the baseline (−15 min), once (21 measurements) at 5, 10, 15 and 20 min after the injection and twice (42 measurements) at 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170 and 180 min after the drug administration.

2.4. Assessment of sedation

Degree of sedation was assessed by measuring the ground-to-lip distance (GLD) at each time point before the first walking test. The head height was measured by looking at the position of the nose related to a cm scale previously marked on a sidebar of the horse stock.

2.5. Statistical analysis

Analysis of data was performed by use of SAS 9.4 software for Windows (SAS Institute Inc., Carry, NC, USA). Data were grouped and summarised as means ± SD and expressed as a percentage relative to baseline values. Two-factor analysis of variance (ANOVA) with repeated measures in both factors was carried out. When a significant interaction between both factors was found, a Student's t test for each time point was performed to compare groups, finishing with a repeated measures one-way ANOVA for each drug to assess for differences between time points with a Dunnett test. Values of $P < 0.05$ were considered significant.

Table 1
Values at walk of stride kinematic and coordination variables before (baseline, −15 min) and at 5, 10, 15, 20 and then every 10 min (total period of 3 h) after IV injection (at 0 min) of saline solution (SS) or 0.2 mg/kg of morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

VARIABLE		Speed		SF		SL		REG	
TREATMENT		SS	Morphine	SS	Morphine	SS	Morphine	SS	Morphine
Baseline		100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
Time after administration of treatment (min)	5	97.98 ± 1.94	98.09 ± 4.54	98.7 ± 1.96	103 ± 4.06	99.33 ± 2.26	95.27 ± 3*	94.45 ± 7.86	92.63 ± 15.55
	10	97.71 ± 3.93	100.4 ± 3.85	99.83 ± 0.74	105.5 ± 3.83	97.88 ± 3.76	95.17 ± 1.38*	100.85 ± 10.27	97.95 ± 19.1
	15	100.12 ± 4.98	95.96 ± 6.6	99.59 ± 2.9	103.49 ± 5.22	100.6 ± 4.65	92.84 ± 6.42*	96.86 ± 12.5	94.57 ± 18.93
	20	101.69 ± 5.32	96.3 ± 5.37	99.25 ± 2.52	103.7 ± 6.48	102.46 ± 4.22	93.08 ± 5.95#,*	101.9 ± 6.57	98.32 ± 16.09
	30	102.77 ± 6.93	98.05 ± 1.9	100.28 ± 1.79	102.29 ± 2.62	102.51 ± 6.78	95.94 ± 3.28*	98.09 ± 11.06	94.1 ± 5.54
	40	101.19 ± 3.62	97.08 ± 3	97.55 ± 2.71	102.3 ± 3.27	103.79 ± 4.03	94.97 ± 3.32#,*	98.07 ± 9.98	100.21 ± 12.54
	50	99.58 ± 4.79	97.9 ± 4.67	97.84 ± 1.94	102.97 ± 4.78	101.86 ± 4.87	95.14 ± 3.93*	94.99 ± 15.47	97.96 ± 6.68
	60	98.52 ± 4.48	98.26 ± 6.01	97.74 ± 2.95	103.46 ± 5.14	100.81 ± 3.15	95 ± 4.32*	94.7 ± 7.93	100.13 ± 11.36
	70	97.78 ± 3.1	99.02 ± 5.43	97.55 ± 2.49	104.21 ± 4.12	100.24 ± 2.41	95.1 ± 4.95#,*	96.5 ± 7.55	97.87 ± 8.25
	80	99.41 ± 4.62	97.21 ± 4.51	97.24 ± 2.76	102.72 ± 4.13	102.27 ± 3.56	94.7 ± 3.23*	95.19 ± 13.64	98.51 ± 11.2
	90	99.12 ± 4	97.5 ± 3.3	96.51 ± 2.25	100.86 ± 3.03	102.77 ± 3.88	96.72 ± 3.7#	99.06 ± 5.32	106.99 ± 11.71
	100	96.6 ± 2.01	97.46 ± 3.72	96.96 ± 1.69	100.98 ± 3.15	99.72 ± 3.3	96.57 ± 3.83	92.47 ± 8.72	102.92 ± 11.11
	110	96.18 ± 2.15	98.23 ± 4.17	96.53 ± 1.48	102.77 ± 4.26	99.72 ± 3.06	95.63 ± 2.55*	96.52 ± 6.11	95.09 ± 12.82
	120	97.65 ± 3.75	98.71 ± 4.68	95.92 ± 2.57	100.65 ± 5.04	101.88 ± 3.68	98.11 ± 2.83	90.13 ± 15.6	99.05 ± 5.77
	130	99.7 ± 5.04	99.71 ± 4.61	97.98 ± 2.03	102.21 ± 4.92	101.8 ± 4.94	97.58 ± 1.33	95.78 ± 8.77	102.93 ± 10.91
	140	97.63 ± 2.88	99.13 ± 4.86	97.01 ± 2	102.06 ± 4.65	100.75 ± 4.38	97.15 ± 2.66	93.78 ± 8.9	101.31 ± 11.97
	150	97.13 ± 1.9	98.48 ± 4.36	98.61 ± 2	101.76 ± 4.97	98.54 ± 2.31	96.83 ± 2.75	96.83 ± 6.93	96.47 ± 8.05
	160	97.81 ± 4.39	97.79 ± 4.21	97.19 ± 2.78	100.78 ± 4.27	100.71 ± 3.56	97.13 ± 4.04	97.16 ± 16.64	93.77 ± 11.54
	170	98.24 ± 5.18	98.05 ± 2.12	95.38 ± 3.83	100.84 ± 4.06	103.03 ± 3.39	97.34 ± 3.37#	95.56 ± 9.18	98.25 ± 16.75
	180	102.21 ± 5.65	97.9 ± 4.59	98 ± 3	101.2 ± 5.02	104.32 ± 4.42	96.8 ± 3.05#	104.78 ± 8.11	99.87 ± 10.87

SF = stride frequency, SL = stride length, REG = regularity.
All variables are expressed as a mean percentage ± SD, relative to baseline values.
Significant differences are in bold.
For a given variable, value is significantly ($P < 0.05$) different from saline solution at that time point.
* For a given variable, value is significantly ($P < 0.05$) different from the baseline value at that time point.

Table 2
Values at walk of power variables before (baseline, −15 min) and at 5, 10, 15, 20 and then every 10 min (total period of 3 h) after IV injection (at 0 min) of 0.2 mg/kg of saline solution (SS) or morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

VARIABLE		DVP		PP		MLP		TP	
TREATMENT		SS	Morphine	SS	Morphine	SS	Morphine	SS	Morphine
Baseline		100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
Time after administration of treatment (min)	5	89.97 ± 6.52	103.17 ± 44.75	96.45 ± 5.18	79.29 ± 17.65*	97.6 ± 7.98	100.82 ± 32.83	94.75 ± 5.55	89.8 ± 21.59
	10	90.78 ± 12.09	118.56 ± 39.49	96.45 ± 8.73	87.05 ± 18.44	95.2 ± 19.48	109.91 ± 36.84	93.83 ± 11.64	100.9 ± 23.33
	15	94.87 ± 26.28	107.89 ± 42.4	92.36 ± 11.92	83.95 ± 19.26*	93.45 ± 19.99	100.82 ± 32.83	93.07 ± 18.78	93.26 ± 19.8
	20	106.63 ± 42.42	104.08 ± 28.74	108.83 ± 37.02	79.58 ± 19.03*	100.14 ± 22.3	97.79 ± 26	94.62 ± 17.53	90.57 ± 16.4
	30	102.33 ± 13.22	95.57 ± 26.47	102.78 ± 11.07	83.45 ± 12.46#,*	104.02 ± 10.19	88.7 ± 11.48	102.71 ± 9.75	87.04 ± 10.41
	40	93.12 ± 15.84	94.74 ± 26.44	94.15 ± 12.83	81.78 ± 12.89*	96.96 ± 19.89	100.82 ± 32.83	95.56 ± 15.4	89.24 ± 15
	50	91.65 ± 18.24	98.28 ± 27.03	91.37 ± 12.82	87 ± 14.75	99.33 ± 10.89	91.73 ± 14.24	93.57 ± 11.8	89.88 ± 12.67
	60	92.38 ± 22.61	107.37 ± 32.86	92.69 ± 10.84	90.17 ± 20.03	96.96 ± 19.89	91.73 ± 14.24	93.58 ± 16.08	93.63 ± 16.39
	70	85.43 ± 15.8	113.15 ± 51.3	88.5 ± 16.38	90.9 ± 16.07	96.96 ± 7.06	100.82 ± 26.09	89.94 ± 10.71	97.37 ± 20.15
	80	88.63 ± 14.74	97.36 ± 32.62	90.43 ± 18.98	87.92 ± 16.93	105.78 ± 7.44	91.73 ± 14.24	95.14 ± 13.07	89.71 ± 14.84
	90	82.26 ± 11.13	95.68 ± 29.33	86.56 ± 14.04	88.21 ± 9.26	95.98 ± 8.72	88.7 ± 11.48	87.99 ± 8.46	88.58 ± 10.34
	100	81.57 ± 11.02	95.67 ± 30.86	88.55 ± 11.54	88.9 ± 12.19	93.24 ± 17.23	88.7 ± 11.48	87.86 ± 9.3	88.64 ± 11.42
	110	76.79 ± 13.54	105.77 ± 29.35	83.89 ± 11.03	93.53 ± 17.02	90.51 ± 11.93	101.7 ± 32.19	83.45 ± 8.78	97.85 ± 20.7
	120	71.43 ± 15.27	94.28 ± 19.25	85.29 ± 10.38	91.72 ± 14.69	87.77 ± 13.94	95.84 ± 11.91	81.58 ± 11.22	92.77 ± 10.13
	130	86.68 ± 12.79	105.06 ± 24.17	90.37 ± 10.89	96.13 ± 15.12	102.84 ± 8.07	104.73 ± 39.26	92.99 ± 8.56	100.07 ± 21.17
	140	81.79 ± 14.54	106.3 ± 27.12	87.01 ± 10.4	93.41 ± 18.13	99.54 ± 14.4	102.57 ± 24.64	88.44 ± 11.76	98.27 ± 18.26
	150	86 ± 14.61	98.42 ± 23.29	92.42 ± 9.67	92.68 ± 16.31	100.21 ± 9.56	93.48 ± 12.94	91.75 ± 10.08	93.17 ± 13.38
	160	82.06 ± 15.6	92.68 ± 20.78	93.32 ± 12.28	88.94 ± 14.66	99.9 ± 3.53	100.82 ± 26.09	91.74 ± 10.02	92.35 ± 16.76
	170	75.99 ± 19.16	92.7 ± 22.31	84.19 ± 18	90.5 ± 17.89	99.9 ± 6.33	109.91 ± 36.84	86.56 ± 12.16	94.82 ± 17.22
	180	92.72 ± 25.42	92.12 ± 27.44	98.86 ± 6.55	91.89 ± 19.85	98.92 ± 8.56	91.33 ± 10.57	96.38 ± 9.87	90.06 ± 14.95

DVP = dorsoventral power, PP = propulsion power, MLP = medio-lateral power, TP = total power.
All variables are expressed as a mean percentage ± SD, relative to baseline values.
Significant differences are in bold.
For a given variable, value is significantly ($P < 0.05$) different from saline solution at that time point.
* For a given variable, value is significantly ($P < 0.05$) different from the baseline value at that time point.

3. Results

All the animals completed the study and no data were removed from the statistical analysis. Administration of 0.2 mg/kg of morphine to healthy horses produced limited effects on the accelerometric parameters investigated when compared to baseline values. Parameter values at baseline and 5, 15 and every 15 min over a period of 3 h and statistical significance are presented in Tables 1–4.

3.1. Stride kinematic variables

Significant statistical differences between both treatments were observed for SL values ($P = 0.0049$) with a greater reduction in the morphine group. Compared with the effect of saline solution, significant differences were observed 20, 40, 70, 90, 170 and 180 min after morphine administration and, when compared to baseline values, SL values were significantly reduced for 80 min and

Table 3
Values at walk of force of acceleration and components of total power before (baseline, −15 min) and at 5, 10, 15, 20 and then every 10 min (total period of 3 h) after IV injection (at 0 min) of saline solution (SS) or 0.2 mg/kg of morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

VARIABLE		F		%DVP		%PP		%MLP	
TREATMENT		SS	Morphine	SS	Morphine	SS	Morphine	SS	Morphine
Baseline		100 ± 0	100 ± 0	29.66 ± 5.11	30.42 ± 6.94	35.59 ± 7.58	36.17 ± 7.06	34.75 ± 6.03	33.41 ± 9.75
Time after	5	96.77 ± 6.59	91.01 ± 18.67	28.11 ± 4.64	32.54 ± 4.2	36.12 ± 6.91	31.66 ± 3.83*	35.77 ± 6.46	35.8 ± 2.54
administration	10	96.05 ± 11.22	100.26 ± 22.25	28.61 ± 4.77	34.37 ± 5.36	36.49 ± 6.33	31.04 ± 4.56#,*	34.9 ± 7.14	34.59 ± 3.79
of treatment	15	92.48 ± 15.22	97.1 ± 19.31	29.66 ± 4.34	33.35 ± 5.11	35.65 ± 6.88	32.07 ± 4.4*	34.69 ± 5.77	34.58 ± 4.79
(min)	20	92.71 ± 14.94	93.9 ± 15.96	32.61 ± 10.52	33.98 ± 6.38	41.12 ± 15.09	31.01 ± 2.88*	36.83 ± 8.21	35.01 ± 6.55
	30	100.09 ± 8.86	88.8 ± 10.9	29.36 ± 4.58	32.18 ± 5.72	35.46 ± 6.7	34.4 ± 6.1	35.18 ± 6.02	33.42 ± 6.79
	40	94.16 ± 12.76	91.88 ± 15.07	29.39 ± 3.4	31.23 ± 4.61	35.05 ± 6.5	32.9 ± 5.14	35.28 ± 8.27	35.87 ± 5.43
	50	93.84 ± 9.81	91.82 ± 12.58	28.5 ± 2.59	32.09 ± 4.93	34.52 ± 6.45	34.71 ± 6.07	36.98 ± 6.6	33.21 ± 5.45
	60	94.78 ± 14.67	95.25 ± 15.94	28.62 ± 2.92	33.54 ± 5.21	35.38 ± 6.2	34.34 ± 5.6	36.01 ± 7.96	32.12 ± 5.64
	70	91.76 ± 10.43	97.93 ± 16.94	27.82 ± 4.81	32.88 ± 4.08	34.46 ± 6.39	33.83 ± 6.41	37.72 ± 7.75	33.3 ± 3.93
	80	95.46 ± 9.97	92.18 ± 14.1	27.66 ± 5.62	31.54 ± 5.35	33.3 ± 6.55	35.16 ± 6.41	39.04 ± 7.56	33.31 ± 4.84
	90	88.79 ± 8.1	90.78 ± 9.33	27.64 ± 4.9	31.37 ± 4.28	34.37 ± 5.11	35.95 ± 6.8	37.99 ± 6.84	32.68 ± 6.12
	100	90.96 ± 9.59	91.16 ± 13.57	27.55 ± 5.32	31.3 ± 5.23	35.62 ± 6.69	36.08 ± 6.57	36.82 ± 8.78	32.62 ± 5.5
	110	86.76 ± 9.23	99.26 ± 18.36	26.94 ± 3.73	31.92 ± 5.22	35.42 ± 6.16	34.73 ± 7.14	37.64 ± 6.7	33.35 ± 5.86
	120	83.33 ± 8.68	93.89 ± 7.92	25.64 ± 4.3	30.5 ± 7.18	36.92 ± 5.79	35.46 ± 6.89	37.44 ± 7.56	34.05 ± 8.35
	130	93.26 ± 7.84	100.1 ± 18.69	27.27 ± 2.55	31.37 ± 5.3	34.42 ± 6.75	35.17 ± 8.18	38.31 ± 6.3	33.46 ± 7.76
	140	90.42 ± 10.46	98.82 ± 15.51	27.34 ± 4.83	32 ± 5.2	35.25 ± 8.65	34.24 ± 6.55	39.11 ± 7.12	33.76 ± 5.62
	150	94.38 ± 10.08	94.43 ± 11.32	27.4 ± 3.32	31.36 ± 5.67	35.37 ± 7.27	35.74 ± 6.63	38.08 ± 6.59	32.89 ± 6.56
	160	93.66 ± 7.92	94.19 ± 14.57	26.04 ± 3.27	30.01 ± 5.62	35.86 ± 6.05	34.79 ± 6.57	38.11 ± 6.83	35.2 ± 6.12
	170	87.9 ± 9.57	96.56 ± 16.65	25.38 ± 3.45	29.06 ± 4.95	33.97 ± 6.22	34.28 ± 6.28	40.65 ± 8.12	36.66 ± 5.4
	180	94.3 ± 8.25	91.74 ± 12.59	27.66 ± 2.88	30.02 ± 4.88	36.39 ± 6.45	36.6 ± 7.33	35.95 ± 7.82	33.38 ± 6.4

F = force of acceleration, %DVP = dorsoventral component of the power, %PP = propulsion component of the power, %MLP = mediolateral component of the power.
F values are expressed as a mean percentage ± SD, relative to baseline values.
Significant differences are in bold.
For a given variable, value is significantly ($P < 0.05$) different from saline solution at that time point.
* For a given variable, value is significantly ($P < 0.05$) different from the baseline value at that time point.

Table 4
Values of ground-to-lip distance before (baseline, −15 min) and at 5, 10, 15, 20 and then every 10 min (total period of 3 h) after IV injection (at 0 min) of 0.2 mg/kg of saline solution (SS) or morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

VARIABLE		GLD	
TREATMENT		SS	Morphine
Baseline		100 ± 0	100 ± 0
Time after	5	102 ± 6.2	98 ± 8.53
administration of	10	96.67 ± 7.31	100.33 ± 4.63
treatment (min)	15	100.83 ± 2.86	98 ± 5.18
	20	104.67 ± 6.83	98.83 ± 6.18
	30	103 ± 6.07	95.83 ± 8.18
	40	101.83 ± 10.74	94.67 ± 6.35
	50	104.17 ± 5.88	100 ± 6.99
	60	102.17 ± 9.06	101 ± 7.72
	70	100.17 ± 10.23	93 ± 8.37
	80	105.33 ± 9.29	95.33 ± 9.75
	90	96.17 ± 10.93	92 ± 7.18
	100	102.17 ± 6.43	95.83 ± 4.67
	110	99.33 ± 6.62	94 ± 8.65
	120	102.83 ± 4.07	96.17 ± 5.31
	130	101 ± 4.52	95.67 ± 6.92
	140	102 ± 6.16	95 ± 3.74
	150	105.5 ± 6.02	95.17 ± 2.64
	160	105 ± 6	95.33 ± 5.65
	170	105 ± 5.93	95.33 ± 2.42
	180	100.83 ± 7.81	96.67 ± 3.78

GLD = ground-to-lip distance.
GLD values are expressed as a mean percentage ± SD, relative to baseline values.

again 110 min after injection of the opioid. No significant differences among speed ($P = 0.1200$) and SF ($P = 0.4195$) values were observed (Table 1).

3.2. Coordination variable

No significant differences among values were observed for regularity ($P = 0.5781$) after administration of morphine (Table 1).

3.3. Energetic variables

A significant reduction was observed for propulsion power values ($P = 0.0076$) (Fig. 1) but not for dorsoventral ($P = 0.3387$), mediolateral ($P = 0.5184$), TP ($P = 0.2295$) or force of acceleration ($P = 0.4139$) values. Compared to saline solution, reductions in propulsion power values appeared only 30 min after morphine administration ($P = 0.0047$) and a significant reduction was observed between baseline values and values obtained 5, 15, 20, 30 and 40 min after administration of 0.2 mg/kg of morphine. A mild alteration of the three-axial power distribution was observed with a significant decrease in the propulsion power ($P = 0.0135$) (Fig. 2) lasting 20 min when compared to baseline values. The dorsoventral and mediolateral parts of the power did not significantly change after the drug administration (Table 2 and 3).

3.4. Sedation variable

No significant reduction was observed for GLD ($P = 0.6915$) following morphine hydrochloride treatment (Table 4).

4. Discussion

It has been described that opiate administration produces a significant increase in locomotor activity and that this effect depends on the dose and the drug administered, with this response being less marked after administration of k-opioid agonists than that seen with morphine and other μ-agonists [1,5]. In the present study, administration of 0.2 mg/kg of morphine hydrochloride only produced, in pain-free horses, mild alterations of the accelerometric variables measured while walking. SL, PP and %PP were the only accelerometric variables, among the 12 studied, which did significantly decrease after opioid administration. These results confirm the hypothesis of minimal effects on locomotor activity after administration of a 0.2 mg/kg dose. Similar results were described with no effect of time or treatment on locomotor activity as mea-

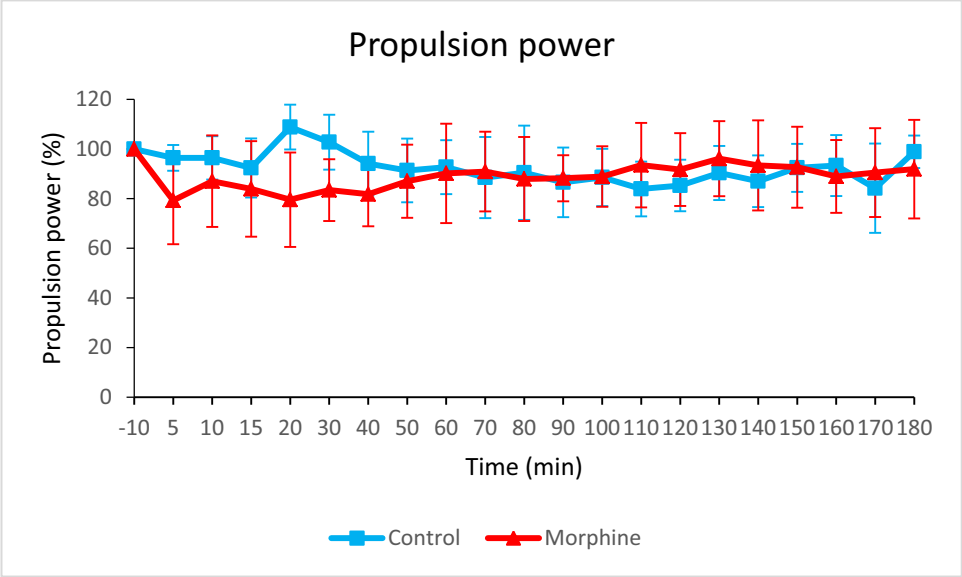

Fig. 1. Propulsion power values (% ± SD) at baseline (−15 min) and 5, 10, 15, 20 and every 10 min during a total period of three hours after IV injection (at 0 min) of saline solution and 0.2 mg/kg of morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

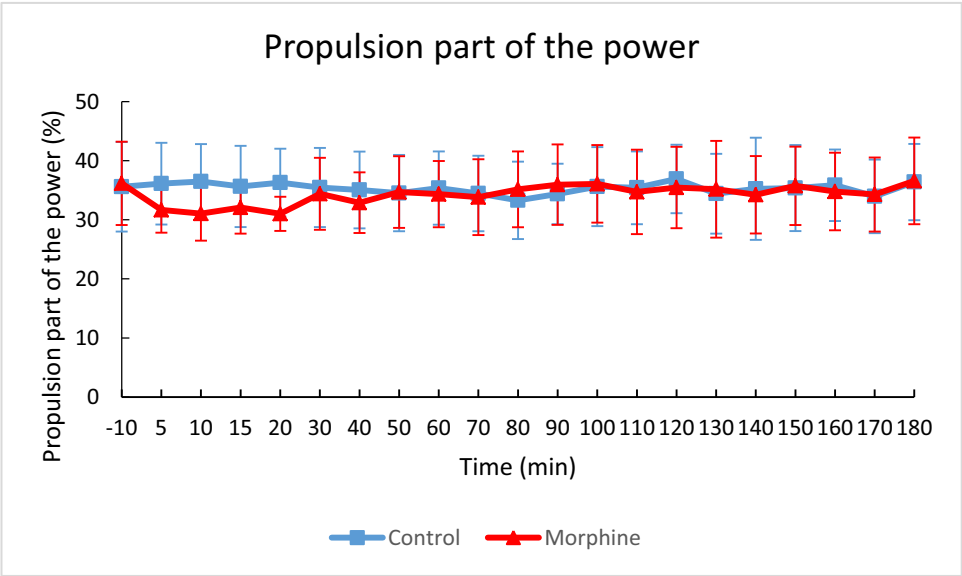

Fig. 2. Propulsion part of the power values (%) at baseline (−15 min) and 5, 10, 15, 20 and every 10 min during a total period of three hours after IV injection (at 0 min) of saline solution and 0.2 mg/kg of morphine hydrochloride solution diluted in saline solution to a volume of 10 mL.

sured using a commercially available three-axis accelerometer in horses after IM or SC administration of meperidine [15].

One of the significantly reduced variables, SL, is linked to speed and is deduced from the relationship between speed and SF, with velocity being the product of SL and SF [18]. In an overground situation, SL is the primary contributor to changes in speed of walking horses [23]. A decrease in SL while maintaining velocity necessarily needs to be associated with an increase in SF. In the present study, the reduction in SL did not change velocity, possibly because the reduction, though significant, was not sufficient to cause a decrease in speed. In fact, the maximal decrease occurred 15 min after the administration of morphine, but these values never exceeded 10% of the baseline. In a study using the same measuring system and a similar protocol, the effects of detomidine alone or combined with a narcotic agonist–antagonist determined that SL was longer in the detomidine group than in the combination group, with the shorter SL likely due to the excitement caused by the administration of butorphanol [16,24]. The effect of detomidine and other alpha-2 agonist drugs is completely different and opposite to the opioid changes observed regarding the stride kinematic parameters. Independently of the molecule used and the route of administration, speed was always reduced after the administration of an alpha-2 agonist drug due to a decrease in SF with no effect on SL values [25,26]. Alpha-2 agonist drugs or phenothiazines are administered, combined with opioids, in order to improve the quality of sedation and analgesia while minimising the possible central nervous system excitation [27,28] and additional studies will be necessary to provide evidence of a possible summatory or synergic effect of opioids on the stride kinematics of horses.

A short-stepped gait has been described as an adaptation to maintain balance [22] but in our study regularity was not significantly altered after morphine administration. Regularity is a co-

ordination accelerometry-specific variable that measures the acceleration pattern similarity of successive strides [18,26], being described as a potentially very sensitive parameter to detect and quantify uncoordinated movements at the walk [7]. Administration of butorphanol produced a bimodal behavioural response with an initial period (within min) of somnolent ataxia followed shortly thereafter by a more prolonged period of increased locomotion [24] and similar results have been described by other authors after the administration of butorphanol [29]. In a recent study, combined with detomidine, butorphanol induced a greater but not significant decrease in regularity values 5 min after the administration of the combination when compared to the administration of detomidine alone; but, from that moment onwards, the decreases in regularity values were more pronounced in the detomidine group [16]. Additionally, in a recent study, the behavioural and cardiopulmonary effects of a constant rate infusion (CRI) of remifentanil-xylazine for sedation in horses were evaluated and, all horses recovered successfully within 10 min after interruption of the CRI of xylazine and remifentanil, without ataxia [30].

With the results of this study, we can certify that the administration of 0.2 mg/kg of morphine alone does not cause incoordination in pain-free animals and that the administration is safe for animals in terms of coordination of movements.

Regarding the energetic parameters, only the PP and the %PP values were significantly decreased but again not enough to trigger a drop in TP values. As previously described, this reduction in propulsive values could be secondary to changes in weight bearing and symmetry [31], produced by the excitatory effect of morphine. Furthermore, as in the SL values, the drop in PP values, although significant, was minimal. The behaviour of PP and %PP values were, once more, opposite to the changes produced by alpha-2 agonist drugs and acepromazine maleate [13,25,26]. In either case, PP values were altered while DVP, MLP and TP values were decreased after alpha-2 agonists and MLP and TP after acepromazine maleate administration. It is a mystery how these opposing effects could affect the accelerometric variables in horses treated with a combination of these drugs. It is known that opioid excitation could be benefited by the administration of sedatives but, the stable accelerometric values obtained in the present study after the injection of 0.2 mg/kg of morphine, seems to suggest that morphine administration will not significantly affect the obvious effects of sedatives on the gait pattern of horses. Nevertheless, a significant effect has been described by combining detomidine and butorphanol, producing a shorter effect in almost all accelerometric parameters [16] and this could be explained by a possible certain effect of opioids minimising or shortening the effects of sedatives on the gait pattern of horses.

GLD is one of the most frequently used parameters to assess sedation in horses for evaluation of phenothiazines, α2-agonists drugs alone or combined opiates [32,33]. In the present study, no significant differences among values were observed in GLD. After the administration of butorphanol and detomidine, GLD was significantly reduced only for 30 min, while the reduction lasted 60 min after the administration of detomidine alone [16]. This shorter effect could be the result of suppression of the sedative effect by the opiate and agreed with the result of our study with no significant sedative effect of morphine administered to healthy animals. Nevertheless, studies evaluating GLD after administration of pure opiates without other sedatives are lacking.

It could be argued that an important individual variation in responses to morphine treatments was detected, which could be related to the small number of animals used in this study. Marked individual variation in responses to opioids have been widely described [34] and in our study, were only observed in the energetic values' results (power and force values), as can be seen when comparing the lower standard deviation values obtained for the stride kinematic, coordination and sedative parameters. However, this greater variation in energetic values does not seem to be an important study limitation as a lower variation was also observed in the calculated mediolateral, dorsoventral and propulsive parts of power (%MLP, %DVP and %PP), where significant differences were also observed. Regarding the energetic parameters, this was observed only in the PP related values.

The excitatory and locomotor side effects are dose-dependent [5] and have been described as an increase in muscle tone, spontaneous muscle twitching, excitation, agitation, restlessness, incessant circling and a significant increase in the number of recorded steps [1,15,24,35], with these effects being less common when given to horses in pain compared with healthy, pain-free research animals [35]. The use of opioids as analgesics in horses is justified if the benefits outweigh the disadvantages [34] and this is especially true because of the need to have several analgesic drugs to treat pain in horses. In the case of opioids, these excitatory and locomotor side effects would produce measurable alterations using inertial sensors, with this kinetic method being the best choice to objectify them.

5. Conclusion

The administration of 0.2 mg/kg of morphine to conscious healthy horses, with the accelerometer positioned in the sacral region during walking, produced limited effects on the accelerometric parameters investigated when compared to baseline values. The described increase of locomotor activity produced by morphine seems to be minimal at this dose and not an important concern for administration of analgesia in a clinical setting.

Conflicts of interest

None of the authors have any financial or personal relationships that could negatively bias the content of the manuscript.

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Supplementary materials

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