The effect of oxytocin or carbetocin administration during mid-diestrus on the interovulatory interval and estrous behavior of mares

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Abstract

Estrous behavior can negatively impact performance mares. Prolongation of the interestrus interval (IEI) or interovulatory interval (IOI) through oxytocin (OXY) injections represents a safe, reversible means of controlling estrous behavior. The purpose of this study was to determine whether an OXY analog, carbetocin (CARB), would increase the IOI and IEI similarly to OXY. We hypothesized that mares would have a longer IOI and IEI after treatment with OXY or CARB than they would during untreated cycles.

Twelve cycling mares were randomly assigned to one of two groups (CARB and OXY). One normal cycle was documented in ten mares prior to the study and two mares after the study. During the treatment cycle, mares were administered either 1.19 mg of CARB or 60 IU of OXY once daily by intramuscular (IM) injection between day seven and 14 post-ovulation. Blood was drawn from all mares once weekly for progesterone assay. Mares were teased with a fertile stallion every other day to detect estrous behavior and subsequently examined by ultrasonography to detect ovulation between May and August.

Administration of CARB decreased the IOI in all mares compared to the control cycle (18±1.1 vs. 20.8±1.8 days, respectively; P=0.00001). Administration of OXY increased the IOI in four of six mares (67%) compared to the control cycle (37.3±17 vs. 21.8±1.5 days, respectively; P=0.0025) and substantially delayed the return of estrous behavior in two of six mares (33%). Two mares failed to return to estrus before the end of the study; the diestral length at that time was used for calculations. Luteal regression and subsequent ovulation were confirmed with serum progesterone concentration after treatment in both groups.

This work suggests that CARB, an analog of OXY, would not be useful for initiating long-term estrus suppression in the mare.

Keywords: Mare, estrus suppression, oxytocin, carbetocin, interestrus interval, luteal function

Introduction

Estrous behavior in mares can be problematic especially during training and performance activities. The mare's reproductive cycle is approximately 21 days in length and estrus expression can vary between five and seven days of the cycle. Many methods for the suppression of estrous behavior have been explored, but no single, highly effective treatment for long term estrus suppression is available.

Methods of estrus suppression available today are administration of exogenous progesterone, suppressing ovarian follicular activity, extending the duration of corpra luteal function, and ovariectomy.[1] Administration of natural progesterone is very effective in suppression of estrus, but due to the inconvenience of daily dosing, tissue reactions and pain associated with daily injection, it is not routinely used.[2] The only effective progestin for estrus suppression in the United States is altrenogest. Altrenogest is administered orally once daily and has been successful in suppressing estrous behavior in 94% of treated mares.[3] Several other synthetic progestins, such as medroxyprogesterone acetate, hydroxyprogesterone caproate, norgestomet and megesterol acetate are available, but lack efficacy.[2,4,5] Presumably, this is due to failure to bind adequately to the progesterone receptors in the mare.[4] Finally, administration of exogenous progestins to competition horses is not permitted by many governing bodies.

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Suppressing the ovarian follicular activity by vaccination against gonadotropin releasing hormone (GnRH) has also been demonstrated. Mares vaccinated with an anti-GnRH vaccine four weeks apart had suppressed follicular development and lower progesterone levels than unvaccinated animals.[6] Mares in this study demonstrated reduced estrous behavior for a minimum of three months before returning to normal cyclicity by the following breeding season. However, GnRH vaccines are currently not approved for use or widely available in the United States. In addition, concern has arisen that GnRH vaccine-induced suppression of ovarian activity could be permanent, which obviously has dire implications for the subsequent fertility of mares treated in this manner.[7]

Another method for long-term estrus suppression is a bilateral ovariectomy. Research has shown a success rate of 82% in estrous behavior reduction in one study, and in another study client satisfaction was 78%.[8-10] However, due to the permanent nature of the procedure, success rates, and surgical risks this is not an appealing solution for long-term estrous suppression.

Extension of luteal function through the use of intrauterine devices, such as glass or plastic balls, has met with variable success rates.[11,12] Another non-pharmacologic technique for prolonging luteal function is the manual disruption of conceptus development beyond day 16 of ovulation.[13] In that study, the mares did not return to estrus for an average of 82 days. Due to the relatively invasive nature of these techniques and a high degree of variability in effectiveness, they have not gained wide acceptance as long-term treatment methods for estrous suppression in mares.

Recently, an alternate means of extending luteal function pharmacologically has been sought by several research groups. Hedberg and coworkers induced a prolonged luteal phase in a limited number of mares by inducing mid-diestrus ovulation after administration of human chorionic gonadotropin (hCG),[14] while work in Allen's laboratory demonstrated prolongation of the luteal phase for at least 30 days after intrauterine administration of 1 mL of various plant oils.[15] The use of OXY to disrupt normal luteolysis was first described by Stout and Allen.[16,17] Subsequent work demonstrated that twice daily injections of 60 IU OXY during the mid-luteal phase disrupted luteolysis by prolonging luteal function in 100% of mares.[10] Further work, comparing once daily and twice daily injections of OXY found no difference between groups with prolonged luteal function in 63% and 71% of animals, respectively.[18] In each of these studies, progesterone levels were measured as a means of determining the length of luteal maintenance.

Although CARB has not been used widely in equine medicine, its use has recently been studied in other species as a long-acting analogue of OXY. Early work in rats demonstrated that CARB and its metabolites bind to myometrial receptors similarly to OXY and have similar effects, although the maximal contractile effects were approximately 50% lower than those of OXY.[19] In women, CARB has been used in the treatment of life-threatening postpartum hemorrhage. In one study, CARB had greater efficacy, increased half-life and a decreased administration frequency when compared with OXY.[20] A study in cattle found no difference between groups in the incidence of postpartum endometritis after administration of saline, OXY or CARB.[21] Recent work in our laboratory demonstrated that the half-life of this OXY analogue was 17.2 minutes,[22] whereas previous work found a half-life of 6.8 minutes for OXY.[23]

Thus, the objective of the current study was to compare the reproductive effects of OXY and CARB administration in cycling mares. The first aim was to determine whether once daily administration of CARB would effectively prevent luteolysis, similarly to OXY. The second aim was to determine whether either OXY or CARB would effectively inhibit estrous behavior in mares, by assessing both endocrine patterns and behavioral patterns in treated and untreated cycles. We hypothesized that the IOI and IEI would be significantly prolonged in mares administered 1.19 mg of CARB or 60 IU of OXY once daily for eight days during diestrus, when compared to a control cycle.

Materials and methods

Mares

Twelve cycling horse-mares between the ages of three and 20 years were enrolled in the study. Eight of the mares were maintained on pastures at the North Carolina State University Veterinary School and four of the mares on pasture at the Equine Educational Unit in Raleigh. Baseline inclusion data were gathered on each mare, including normal physical examination, normal ultrasonographic appearance of the reproductive tract, and a Grade I or IIa endometrial biopsy.[24] Each mare's cyclicity was documented between February and July prior to enrollment into the experiment by transrectal ultrasonography. The IOI of ten mares was documented by repeated transrectal examination during a control cycle before treatment and for two mares it was documented during a control cycle after treatment.

Drug administration

The mares were randomly assigned to one of two experimental groups, (CARB or OXY). Mares in Group OXY received 60 IU of OXY (Osborn®, Bimeda Inc., Le Sueur, MN) once daily between day seven and 14 post-ovulation as previously described.[18] Mares in Group CARB received 1.19 mg of CARB (Hypophysine LA®, Veyx-Pharma GmbH, Schwarzenborn, Germany), administered once daily between day 7 and 14 post-ovulation. Based on the pharmacokinetics, 0.175 mg of CARB is equivalent to 8.75 IU of natural OXY; therefore, 1.19 mg CARB is equivalent to 60 IU OXY.[22] Both medications were administered via intramuscular injection in the morning. The injection sites were alternated between neck and hip muscles on each day. Body temperature, heart rate, and respiration rate were recorded immediately before each injection and again 20 minutes after injection. Any signs of discomfort or reactions were noted.

Teasing

Normal estrous behavior of each mare was documented by teasing to a fertile stallion before enrollment into the study. During control and the treatment cycles, mares were teased to a fertile stallion on Monday, Wednesday and Friday, beginning seven days after ovulation and ending when the mare exited the subsequent estrus or at the conclusion of the study on August 15th. Behavioral response was given a score of 0 to 4 based on a model described by Gorecka and coworkers.[25]

Behavioral evaluation scores

- Score 0: Non-receptive behavior
- Score 1: Mare standing still indifferently (passive)
- Score 2: Mare shows both estrous behavior and some non-receptive behavior
- Score 3: Mare shows full estrous behavior and some non-receptive behavior
- Score 4: Mare shows full estrus: no non-receptive behavior

The IEI was calculated from the day of ovulation until the first day that mares were given a behavior score of 2 or greater.

Ultrasonography

When a behavioral score of 1 or greater was documented (standing passively, lifting tail, clitoral eversion, approaching stallion with pricked ears, frequent urination, and immobility in presence of stallion), mares were evaluated via transrectal ultrasonography once daily to confirm the physiological characteristics of estrus and to monitor the dominant follicle until ovulation (disappearance of the dominant follicle and presence of a corpus luteum). At each evaluation, the firmness of the cervix was noted and the amount of uterine edema was scored as previously described by Samper and coworkers.[26] The presence of any abnormality was also documented. Ultrasonographic diagnosis of ovulation was used to determine the IOI for control and treatment cycles.

Blood sample collection

Blood samples were collected from the mares every Thursday after onset of treatment for the detection of progesterone (P4) until ovulation of the dominant follicle. Seven mLs of blood were collected from alternating jugular veins into evacuated glass tubes (BD Vacutainers ®, BD, Franklin Lakes NJ) with no additive. All blood samples were kept at room temperature (22°C) until clotted and were centrifuged at 3,000 revolutions per minute for three minutes. The serum was recovered and stored at -80°C until all samples were collected for analysis.

Radioimmunoassay for progesterone

Quantification of serum P4 levels was performed using a solid phase-radioimmunoassay kit (COAT-A-COUNT total progesterone kit, Siemens Medical Diagnostics, Los Angeles, CA). The kit was validated for measuring P4 in equine serum in our laboratory.[27]

Statistical analysis

Data were evaluated for normality using a Shapiro-Wilk Normality test. Homogeneity of variance was examined between groups using an F-test. Differences in interestrus and IOI were compared between cycles using either a paired t-test or Wilkoxon Signed Rank test, and between groups using a two-sample Student's t test or Wilkoxon Rank Sum test, depending on the results of the Shapiro Wilk test. The software-program Statistix 8.1 (Statistix®, Analytical Software Inc, Tallahassee, FL) was used to analyze data. Significance was assigned to all values $P \leq 0.05$.

Results

Interovulatory interval

The IOI of both cycles was determined precisely in six of six mares in Group CARB and five of six mares in Group OXY. One mare in Group OXY experienced an ovulation without demonstrating behavioral estrus during the treatment cycle and the exact ovulation date was unknown. The last examination at which she did not have a corpus luteum was used for analysis (53 days). Mares in Group CARB had an IOI of 20.8 ± 1.8 days in the control cycle and an IOI of 18.0 ± 1.1 days in the treatment cycle (P=0.00001). Six of six mares in group CARB had a shorter IOI after treatment than during the control cycle, with a reduction in IOI of one to five days. Mares in Group OXY had an IOI of 21.8 ± 1.5 days in the control cycle and 37.3 ± 17 days in the treatment cycle (P=0.0025). Four of six mares (67%) had a longer IOI after treatment than during the control cycle, with an increase of five to 52 days. One mare had no numerical change in IOI between cycles and one mare had a slight numerical decrease in IOI after treatment (one day). Mares in Group CARB had significantly shorter IOI during the treatment cycle than mares in Group OXY (P=0.0043). No differences were detected in the IOI between control cycles of either group (P=0.3; Figure 1).

Interestrus interval

The IEI of both cycles was determined precisely in six of six mares in Group CARB and four of six mares in Group OXY. Two mares in Group OXY had not demonstrated any signs of estrus at the conclusion of the study and the interval from the onset of the cycle to the study conclusion (68 and 69 days) was used for statistical purposes.

Mares in Group CARB had an IEI of 15.3 ± 6.2 days in the control cycle and 13.0 ± 1.1 days in the treatment cycle (P=0.0025). One mare in this group showed mild signs of estrus during diestrus in both the treatment and control cycle. She first had a behavioral score of 2 three days after ovulation during the control cycle and 12 days after ovulation during the treatment cycle. All other mares had a slight numerically shorter IEI in the treatment cycle, compared to the control cycle (two to seven days). Mares in Group OXY had a mean IEI of 14.8 ± 5.9 days in the control cycle and 33.2 ± 27.7 days in the treatment cycle (P=0.0025). One mare showed behavioral estrus intermittently during diestrus of both the treatment and control cycle. This mare first had a behavioral score of two or greater on day 3 of the control cycle and day 8 of the treatment cycle. She continued to show intermittent estrus (scores 2-4) until the subsequent ovulation at 62 days. Two mares (33%) in Group OXY failed to show estrus before the conclusion of the study (68 and 69 days, respectively). Each of these mares experienced a second ovulation during this period in the absence of estrous behavior. Four mares (67%) had an IEI of similar length after treatment as on the control cycle (Figure 2). Mares in Group CARB had numerically, but shorter IEI during the treatment cycle than mares in Group OXY, which was not statistically significant (P=0.07).

Progesterone

Luteolysis was confirmed by a serum progesterone concentration <1 ng/mL in six of six mares in Group CARB by week 2 after treatment onset. Further, corpus luteum formation was confirmed by an increased serum progesterone concentration at subsequent measurement in five of five mares in Group CARB. The sample from the sixth mare was lost during processing. In Group OXY, luteolysis was confirmed by measurement of serum progesterone concentrations <1 ng/mL by week 2 in two mares and by week 3 in an additional mare. A subsequent rise in serum progesterone concentrations confirmed ovulation and luteal development in all three of these mares. In one mare, progesterone concentrations remained above 1 ng/mL for eight weeks post-ovulation. This mare displayed intermittent estrus throughout the study despite serum progesterone concentrations consistent with diestrus (2.4-11.1 ng/mL). In two mares, serum progesterone concentrations remained above 1 ng/mL for the duration of the study (nine and 12 weeks, respectively). Each of these mares had a secondary ovulation between week seven and week 11 after treatment onset in the presence of elevated progesterone concentrations (5.1-8.8 ng/mL) and without demonstrating any behavioral signs of estrus.

Drug-related complications

In Group CARB, one mare showed slight bleeding at two of eight injection sites. In four of six mares there was moderate to severe sweating over the neck, flank, and axilla regions.

In Group OXY, one mare displayed mild sweating. One mare displayed urticaria around the site of injection after the first two injections. One mare had an onset of mild diarrhea after the second injection which continued a few days after the completion of the last injection; no elevation in body temperature was noted.

Physical examination

Body temperature, heart rate and respiratory rate were not different 20 minutes after administration of either CARB or OXY than immediately before drug administration (Figure 3).

Discussion

The results of this study demonstrate that both OXY and CARB can be administered safely during mid-diestrus at relatively high doses (60 IU and 1.19 mg respectively) without notable side-effects. This is an important consideration for owners and veterinarians seeking a medical option for estrus suppression.

CARB, an OXY analog, administered once daily between days seven and 14 post-ovulation did not increase either the IOI or IEI. Contrary to our hypothesis, CARB administration resulted in a statistically significant decrease in the IOI and IEI, compared to a control cycle. During the treatment cycle, 100% (six of six) of mares administered CARB had a shorter IOI than during the control cycle, and 83% (five of six) of mares had a shorter IEI.

OXY administration increased the IOI and IEI compared to the control cycle. During the treatment cycle, 67% (for of six) of mares had a longer IOI, with a delay in ovulation by five to 52 days compared to the control cycle. These findings are similar to those previously published by Vanderwall and coworkers.[18] Interestingly, only 33% (two of six) of mares had a prolonged IEI of greater than 30 days after OXY treatment, whereas 67% (four of six) had an IEI of similar length during the control and treatment cycles. This suggests that while the differences were statistically significant, OXY treatment may not effectively inhibit unwanted estrous behavior in a majority of mares.

Most previous work has focused on hormonal effects of OXY administration, and little information is available regarding behavioral effects. One recently published study utilized a protocol similar to the one described here and found "a strong agreement between teasing behavior, ultrasonographic assessment of ovarian activity, and concentration of progesterone in serum".[5] In that study, three groups of six mares were subjected to eight injections of either serum, 10 IU OXY IM or 10 IU OXY IV. Mares were subsequently monitored for behavioral estrus via teasing three times weekly, and for ovulation via transrectal ultrasound examination and serum progesterone assays. Gee and coworkers reported that mares administered OXY IV had a longer duration of diestrus than control mares, but the proportion of mares in which diestrus was greater than 30 days was not statistically different between groups (5/6, 1/6 and 2/6 for the IV, IM and control groups respectively).[5] Similarly, in the current study, IM administration of OXY (60 IU once daily for eight days) delayed the return to estrus in only two of six mares. Two mares in this study (one each from Group CARB and OXY), demonstrated estrus behavior during diestrus in both the control and treatment cycle, despite the fact that they had an ultrasonographically visible corpus luteum and adequate serum progesterone concentration to inhibit estrus. These mares may have been displaying submissive behavior in response to close contact with a stallion. It has been shown that submissive mares may show similar behaviors similar to estrus when placed in a stressful situation including urination and winking.[28] Although OXY administration did result in an increased IOI (from 23 to 62 days) in one of these mares, it did not eliminate estrus behavior. Several questions remain at the conclusion of this study; it is unclear whether the estrous behavior demonstrated in response to direct contact with a stallion would also result in disruptive behavior in a performance setting. It is possible that OXY administration would result in adequate behavioral control in a performance setting without completely preventing them from "teasing" in response to direct contact with a stallion. Furthermore, it has been suggested that some mares have impaired racing or show performance due to discomfort or pain from a large preovulatory follicle rather than directly from estrous behavior (Bailey, unpublished data). In three of four mares with an increased IOI in this study, the presence of a large follicle or diestrus ovulation was documented. It is possible that these would result in decreased performance. A large randomized clinical trial of mares in training would be necessary to evaluate such effects.

Luteolytic mechanisms have been well-studied in mares and were reviewed in detail by Shand.[29] Briefly, Goff and coworkers demonstrated an increase in prostaglandin metabolites in the peripheral circulation of mares administered OXY after day 11 post-ovulation, with a peak response between 14 and 16 days.[30] Subsequently, work by Stout and coworkers demonstrated that continuous intravenous administration of OXY, initiated prior to this period, could inhibit luteolysis, whereas initiation of treatment during this period hastened ovulation in two of five animals.[16] A series of studies have strongly suggested that a major source of endogenous OXY for the induction of luteolysis is the endometrium itself.[31-34] The biologic importance of uterine OXY for luteolysis was confirmed by Stout and coworkers, who demonstrated that intrauterine infusion of OXY around the time of luteolysis resulted in a substantial rise in peripheral prostaglandin metabolites in the absence of elevated systemic OXY concentrations.[16,32] The mechanism by which diestrus administration of OXY inhibits luteolysis is not fully understood. Based on the information regarding luteolysis in the mare, it has been presumed by our group, as well as others, that mid-diestrus OXY administration to mares may prevent the increase in endometrial OXY receptor numbers or an increase in endometrial OXY receptor responsiveness, normally observed in diestrous mares.[17,18]

The prolonged luteal phase seen in many diestrus mares administered OXY in this study and several others has been presumed to result from a negative feedback loop, preventing the upregulation of OXY receptors in the uterus, as first proposed by Stout.[17,18] Failure of CARB to induce a prolonged luteal phase could also indirectly support this, as a previous study demonstrated that CARB and its metabolites have both agonist and antagonist effects on OXY receptors.[19] However, Vanderwall and coworkers did not find a difference in endometrial OXY-binding capacity in mares administered OXY or saline twice daily between seven and 14 days.[18] Thus the mechanism by which OXY, but not CARB, disrupts normal luteolysis after mid-diestrus administration is not known at this time. The use of CARB in addition to OXY may serve as a useful model for future research in this area.

In conclusion, the current study demonstrated the safety of both OXY and CARB in the mare, and found the effect of OXY to be similar to previous work. In contrast, CARB administered between seven and 14 days post-ovulation effectively short-cycled the mares and decreased the IOI. Neither CARB, nor OXY reliably inhibited estrous behavior in mares exposed to a mature stallion.

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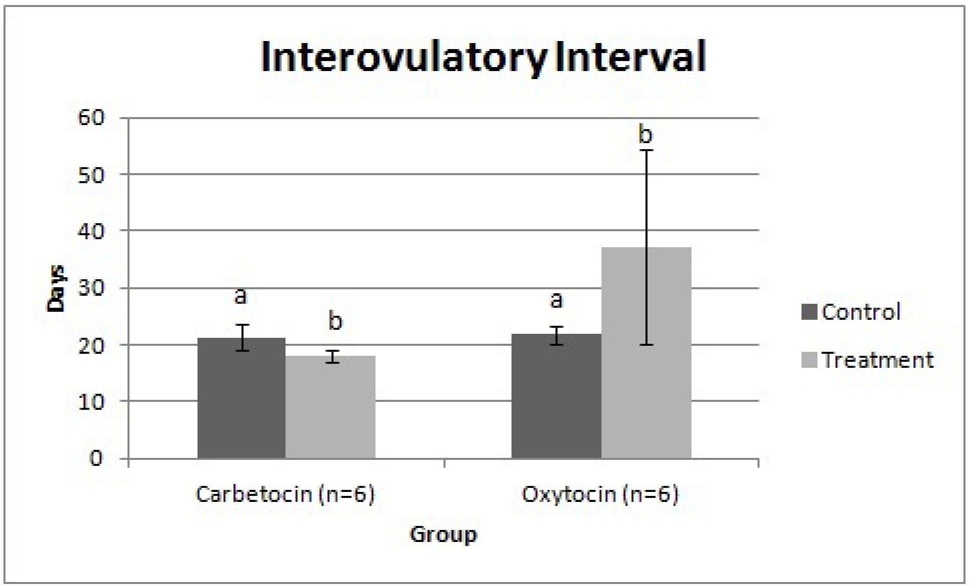

Figure 1. Number of days (Mean±SD) between successive ovulations of mares in Group CARB and Group OXYduring control and treatment cycles. Statistically significant differences between cycles within or between treatment groups are indicated by different letters. The IOI was shorter for treated mares in Group CARB, than during the control cycle (P=0.00001) and longer for treated mares in Group OXY than during the control cycle (P=0.0025). Treated mares in Group CARB had significantly shorter IOI than treated mares in Group OXY (P=0.0043).

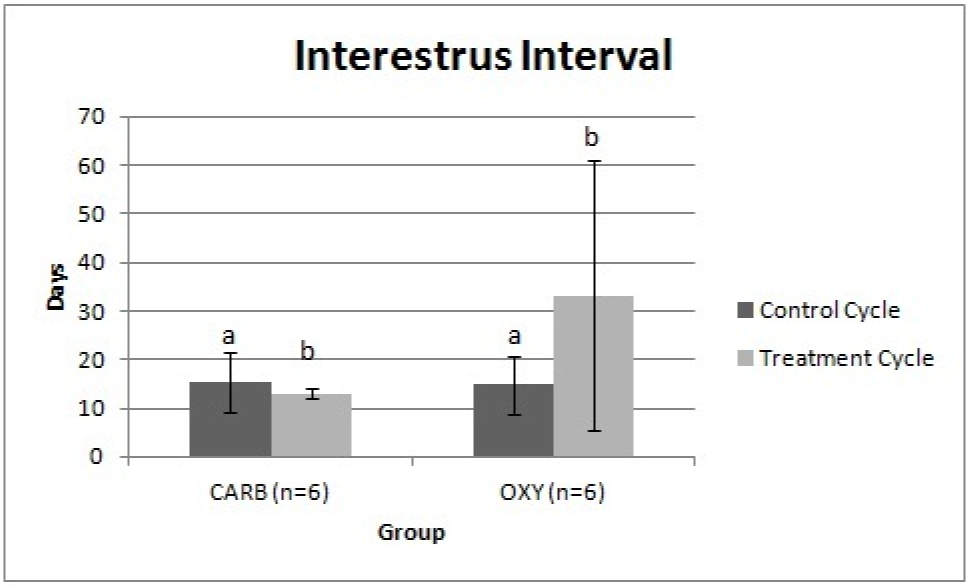

Figure 2. Number of days (Mean±SD) with a behavior score <2 in Group CARB and Group OXYduring control and treatment cycles. Statistically significant differences between cycles within or between treatment groups are indicated by different letters. The IEI was shorter for treated mares in Group CARB, than during the control cycle (P=0.0025) and longer for treated mares in Group OXY than during the control cycle (P=0.0025). Treated mares in Group CARB had a numerically shorter IEI than treated mares in Group OXY (P=0.07).

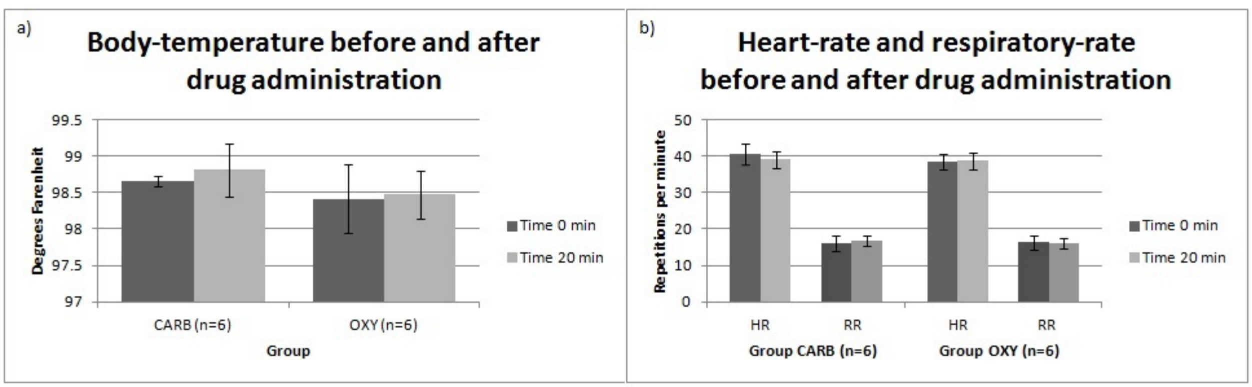

Figure 3. Mean ± SD body temperature (panel a), heart-rate and respiratory rate (panel b) of mares in Group CARB and Group OXY prior to drug administration and 20 minutes later. No differences were detected between groups or at different times in relation to treatment.

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