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Oxytocin treatment does not change cardiovascular parameters, hematology and plasma electrolytes in parturient horse mares

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ABSTRACT

In mares, foaling is associated with changes in hematology, plasma electrolytes, blood pressure and heart rate and it has been hypothesized that these are induced by oxytocin. To test this hypothesis, mares (n = 8–14/group) were treated with oxytocin (OT; 20 I.U.) or saline (CON) at 1 h (test A) and 12 h after foaling (test B) and during first postpartum diestrus (test C). Heart rate, heart rate variability (HRV), atrioventricular blocks, salivary cortisol concentration, blood pressure, plasma electrolytes and blood count were determined. Heart rate decreased from test A to C ($P < 0.001$) but at no time differed between groups. The HRV, blood pressure and occurrence of atrioventricular blocks did not change in response to oxytocin. Cortisol concentration decreased from test A to C ($P < 0.001$). Oxytocin induced a cortisol release in test B (time x treatment $P < 0.001$, time x test $P < 0.001$). Plasma sodium and chloride concentrations decreased from test A to C ($P < 0.001$) but did not differ between groups. In test A, potassium concentration increased in CON but not OT mares (time $P < 0.01$, time x test $P < 0.01$, time x treatment $P < 0.05$). Polymorphnuclear cell (PMN) numbers in blood decreased from test A to C ($P < 0.001$) while lymphocytes increased ($P < 0.05$). At no time PMN and lymphocytes differed between groups. Oxytocin treatment had no effect on skin temperature. In conclusion, except for a limited effect on cortisol release, oxytocin was without effect and the hypothesis of oxytocin-induced alterations in cardiac parameters, plasma electrolytes and hematology of foaling mares was not verified.

1. Introduction

In mares, foaling and the immediate postpartum period are associated with changes in hematology, blood plasma electrolytes, blood pressure and heart rate. Directly before parturition, blood pressure is reduced but increases within an hour after delivery of the foal. At the same time, hematocrit, total protein and sodium and chloride concentrations in plasma increase rapidly [1]. In the majority of foaling mares, repeated atrioventricular (AV) blocks occur during and within 2 h after expulsion of the foal [2]. These events coincide with a phase of marked oxytocin release [3,4].

Oxytocin, besides its effects on myometrial contractions, may also impact on cardiac function, fluid balance, the autonomous nervous system and adrenocortical activity. In parturient women, oxytocin treatment induced a rapid decrease in blood pressure and increase in heart rate [5,6]. Besides a general relaxing effect on vascular smooth muscle, oxytocin has vasoconstrictive effects on coronary vessels [7] and in the isolated rat and dog heart decreased beat frequency and stimulated the release of atrial natriuretic peptide (ANP) [8,9]. Oxytocin caused fluid losses after parturition in rats, both, via ANP and directly [10]. It can also shift autonomous nervous system activity towards parasympathetic dominance in humans, leading to increases in heart rate variability (HRV) and a reduced adrenocortical response to experimental stressors [11,12]. In humans, the combination of hypotension, tachycardia and coronary vasoconstriction may cause a mismatch between myocardial oxygen demand and supply, leading to myocardial ischemia. Therefore, in parturient women, oxytocin is preferably given at low

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doses and administered slowly [6]. In mares, as in women, oxytocin can be used for the induction of parturition [13]. Oxytocin is also the treatment of choice in mares with retained placenta [14]. The half-life of oxytocin in horses is less than 7 min [15,16]. Therapeutic effects thus require either repeated injections at short intervals or continuous infusions. To what extent oxytocin treatment in peripartum mares causes cardiovascular side effects to the best of our knowledge has not been analysed in controlled studies. A clinical case report, however, suggests that infusion of oxytocin in postpartum mares does not change heart rate and heart rate variability (HRV) [17].

In order to investigate effects of oxytocin on cardiovascular function, hematology, plasma electrolytes and cortisol release in the peripartum period, mares were treated with oxytocin or saline 1 h and 12 h after foaling and for comparison also after resumption of ovarian cyclicity postpartum. Heart rate, HRV, the occurrence of AV blocks, salivary cortisol concentration, blood pressure, plasma electrolytes and hematology parameters were determined. We hypothesized that oxytocin induces AV blocks as occur during the expulsive phase of labor, causes an increase in heart rate and decline in blood pressure and has an impact on plasma electrolytes, hematology parameters and cortisol release. If these hypotheses were verified, a more cautious use of oxytocin treatment in peripartum mares might be warranted.

2. Materials and methods

2.1. Animals

A total of 27 warmblood brood mares of the Brandenburg State Stud at Neustadt (Dosse), Germany, were available for the study. Age of the mares was 8.7 ± 0.9 years (3–18 years). Gestation length was 337 ± 1 days (325–351 days). Mares were housed in group stables on straw and were fed oats and hay twice daily. Water was freely available at all times. Housing was changed to individual boxes six weeks before the calculated day of foaling but mares still had daily paddock access together with group mates. In the foaling unit, mares were observed 24 h per day. All mares carried singleton pregnancies. Foaling was supervised by a veterinarian but no obstetrical intervention was needed. Mean time from rupture of the allantochorion until birth of the foal was 14.6 ± 1.9 min and passage of fetal membranes was completed within 49.1 ± 7.4 min after parturition. First suckling of the foals occurred at 129 ± 10 min after birth. All mares and their foals were healthy throughout the study period.

2.2. Experimental design

The study was approved by the competent authority for animal experimentation in Brandenburg State, Germany (*Landesamt für Umwelt, Gesundheit und Verbraucherschutz*, license number: V3-2347-21-2013).

The effect of oxytocin injection was tested 1 h (test A) and 12 h after foaling (test B) and 7 days after the first postpartum ovulation (corresponding to 16.1 ± 0.5 days after foaling, test C). In each test, mares were either treated with oxytocin (OT; 20 I.U., Oxytocin Bengen, Wirtschaftsgenossenschaft deutscher Tierärzte, Garbsen, Germany) or saline (CON; 2 ml, Natriumchloridlösung 0.9% WDT, Wirtschaftsgenossenschaft deutscher Tierärzte) intravenously. For test A, mares were ranked by calculated day of parturition and allocated in alternating order to groups OT (n = 14) and CON (n = 13) and in all mares, groups were changed for test B. For test C, 16 out of the initial 27 mares were available. These 16 mares were ranked by day of first postpartum ovulation and allocated to groups OT (n = 8) and CON (n = 8) in alternating order. Test C experiments were always performed between 6 and 8 a.m.

Blood was collected from one jugular vein into tubes containing either EDTA or heparin (Vacuette, Greiner, Kremsmünster, Austria) for analysis of cortisol, hematocrit, total protein, blood count and plasma electrolytes. Time of injection of either oxytocin or saline was defined as time 0. Blood samples were taken 5 min before treatment and at 5, 15 and 30 min thereafter. Not all parameters were analysed at all time points. Blood pressure was measured with an oscillometric indirect wrist blood pressure monitor and from 5 min before to 30 min after treatment a continuous electrocardiogram (ECG) was recorded. Superficial body temperature was determined by infrared thermography in the left and right flank area of the mares during test B and C. Skin temperature was not measured during test A.

2.3. Blood pressure, heart rate, heart rate variability and cardiac arrhythmias

Blood pressure was determined with an oscillometric non-invasive indirect wrist blood pressure monitor (Breuer Medical, Ulm, Germany) following established procedures [18] as described previously [1]. The cuff of the indirect blood pressure monitor was placed over the middle coccygeal artery and blood pressure was measured starting at 5 min before, directly after and 30 min after oxytocin and saline injections. Each measurement was repeated three times and the mean of these values was used for further calculations.

Electrocardiogram recordings were performed with a portable ECG device (Televet 100, Engel Engineering Service GmbH, Offenbach am Main, Germany) as described for fetomaternal electrocardiography [19] with modifications [20]. In brief, the green electrode was placed on the right side of the horse 3 cm laterally from the sternum in the girth area. The red and black electrodes were attached 20 and 30 cm below the withers on the left side of the thorax. The yellow electrode was positioned similar to the red electrode on the right side of the thorax. From the recorded cardiac beat-to-beat (RR) intervals, heart rate and the time domain HRV parameters SDRR (standard deviation of the RR interval) and RMSSD (root mean square of successive RR differences) were calculated with the Kubios HRV software (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) as described [20,21]. Heart rate and HRV were calculated for consecutive 1 min intervals from 5 min before to 5 min after OT and CON treatments and for 1 min intervals at 15 and 30 min after treatments. Additionally, all ECG recordings were checked visually for the occurrence of cardiac arrhythmias. Second degree AV blocks were identified as described [2] and counted as events within 5 min intervals starting at 5 min before, at time 0 and 15 and 30 min after treatments.

2.4. Cortisol analysis

Blood was centrifuged for 10 min at 1000 g and the plasma aspirated and frozen at −20 °C until analysis. Cortisol concentration was determined with a commercial enzyme immunoassay (Demeditec Diagnostics, Kiel, Germany) validated for equine saliva in the authors' laboratory [22]. The intra-assay coefficient of variation was 6.1%, the interassay coefficient of variation 10.9% and the minimal detectable concentration 0.02 ng/mL. Analysis of cortisol concentration was performed in saliva collected directly before (time 0) and 15 and 30 min after treatments in tests A, B and C.

2.5. Hematology and plasma electrolytes

Analysis of all hematology parameters and plasma electrolytes followed established procedures [1]. Hematocrit was determined