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Effects of oxytocin and carbetocin on farrowing performance

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ABSTRACT

During sow parturition, there is need for an alternative uterotonic to oxytocin with less potency so piglets are not at risk of hypoxia and stillbirth. In this study, there was examination of carbetocin, a longer lasting analogue of oxytocin, and whether the lesser contractile force and duration resulting as a consequence of this treatment would improve piglet survivability. Following delivery of the first piglet, sows were serially assigned by parity to receive injections of 10 IU oxytocin (n = 35), 0.07 mg carbetocin (n = 36), or serve as a non-injected control (n = 30). The incidence of dystocia and stillbirths was recorded. To estimate liveborn piglet viability, umbilical cord blood samples were obtained from pigs 1, 2, 3 and 8, 9, 10, and lactate content was quantified to assess hypoxia during delivery. A blood sample collected at 24 h was assayed for total protein in plasma (%) as an indicator of colostrum intake. Treatment with oxytocin and carbetocin reduced farrowing duration (P = 0.023) and sows treated with carbetocin had piglets with the least umbilical cord blood lactate (P = 0.008) and plasma protein (P = 0.005) concentrations. These data indicate carbetocin has the efficacy to accelerate piglet delivery and reduce piglet hypoxia, although the reason for reduced plasma protein with this treatment remains unexplained.

1. Introduction

Along with appropriate management and nutrition, breeding sows for larger litter size is the primary means to improve overall production yield by increasing the total number of piglets born per sow (Rojo-Gimeno et al., 2016). Although increasing litter size has long been a breeding goal of producers, it has resulted in serious implications for piglet welfare (Rutherford et al., 2013). Larger litter size may result in a prolonged duration of farrowing, which has been associated with an increased incidence of piglet hypoxia (Mota-Rojas et al., 2002) and stillbirths (Oliviero et al., 2010). In attempts to improve farrowing supervision and thereby reduce neonatal piglet mortality (Holyoake et al., 1996; Le Cozler et al., 2002), it is common to administer prostaglandin F2α (PGF) to induce farrowing (Kirkwood, 2015). Additionally, producers often administer oxytocin 24 h after treatment with PGF to induce an earlier delivery of the first piglet (Kirkwood, 2015).

Even though there is the current use of oxytocin as a reproductive aid, the rate of piglet mortalities during and immediately after farrowing is enhanced as a result of this treatment (Mota-Rojas et al., 2005a). The extent of oxytocin-induced contractions is greater which results in a restriction of blood flow to the uterus, impairing placental perfusion and increases the incidence of fetal hypoxia (Mota-Rojas et al., 2005a). Furthermore, the routine administration of oxytocin 24 h after PGF treatments often results in interrupted farrowing, whereby the first piglet is delivered promptly but subsequently there is a delay or cessation of the farrowing process (Kirkwood, 2015). Even though there are these problems, oxytocin continues to be used in pork production enterprises because it is

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inexpensive and more widely known by producers than other potential uterotonic compounds. A suitable alternative to oxytocin would be a treatment which reduces farrowing duration but does not result in the risk of dystocia and stillbirth.

Carbetocin (one-deamino-one-carba-two-tryosine (O-methyl)-oxytocin) is a long acting analogue of oxytocin formulated to stimulate uterine contractions of less intensity and duration. Carbetocin has a similar chemical structure to oxytocin, but with alterations so there is a longer half life in circulation than occurs with oxytocin (Meshykhi et al., 2016). Structural differences to oxytocin include a methyl group in place of a di-sulphide bond and replacement of cysteine with a hydrogen bond. These molecular differences between carbetocin and oxytocin result in carbetocin to having a greater stability and lesser susceptibility to catabolism of the molecule by disulphide and aminopeptide enzymes (Meshykhi et al., 2016). Carbetocin, therefore, has approximately 50% less myometrial contraction efficacy as oxytocin and has a half-life of 41 compared to 1–5 min for oxytocin (Engstrøm et al., 1998; Meshykhi et al., 2016). The structural differences in carbetocin results in prolonged uterine responses compared to oxytocin in both frequency and amplitude of contractions (Su et al., 2012). The aim of the present study is to test the hypothesis that treatment with carbetocin, compared to oxytocin, would accelerate farrowing without resulting in the adverse effects of oxytocin on piglet viability and survival.

2. Matherials and methods

2.1. Animals and management

The study was conducted at the University of Adelaide swine research facility and was approved by the university Animal Ethics Committee. In four replicates, 102 mixed parity Large White x Landrace sows were housed in individual farrowing crates 5 days prior to the due date. The farrowing rooms were maintained at a temperature of 25 ± 2 °C and prior to farrowing sows were fed 3 kg/d of a commercial lactation diet and had free access to fresh water. At 2 days before the expected farrowing date, there was induction of parturition with two 100 µg injections of the PGF analogue, cloprostenol (Juramate®, Jurox Pty, Ltd, Rutherford, NSW, Australia), administered into the vulva 6 h apart. Starting 24 h after the initial PGF treatment, sows were observed continuously until farrowing was complete

2.2. Treatment

At delivery of the first piglet, sows were assigned serially by parity to receive an intramuscular injection of 10 IU oxytocin (Syntocin, Troy laboratories, Glendenning, NSW, Australia; $n = 35$) or 0.07 mg carbetocin (Duratocin®, Ferring Pharmaceuticals, Pymble, NSW, Australia; $n = 36$), or served as non-injected controls ($n = 30$).

2.3. Data collection

Obstetric assistance was provided for sows when the piglet delivery interval exceeded 45 min and was recorded as a dystocia event. The percentage of sows that required this assistance was termed mean dystocia events. For any piglet, where there was an obvious need for assistance (e.g., piglets delivered within foetal membranes), there was respective assistance provided depending on the type of problem and the piglet was placed under a heat lamp. At delivery, piglets were recorded as liveborn or stillborn. Immediately after birth, umbilical-cord blood samples from the first three piglets and piglets eight, nine, and ten in the litter were assayed for lactate concentration as an indicator of peri-parturient hypoxia. Blood lactate concentrations were measured using the EDGE™ handheld blood lactate monitor (Ryan Sports Marketing, Forbes, NSW, Australia). This procedure of choice was determined based on a literature comparison of different machines which resulted in the EDGE™ device having the least total error for quantitation (0–2 mM) of lactate concentrations of less than 15 mM (Bonaventura et al., 2015). At 24–30 h post-farrowing, single blood samples were collected from the same pigs by vena cava puncture into heparinised tubes for determination of total protein concentration. Samples were centrifuged for 10 min at 3000 rpm and total protein content in plasma (%) was determined using a handheld PAL-IOS™ refractometer (Atago PAL-11S, Starr Instruments, Dandenong South, Vic, Australia). In the laboratory where the procedures for the present research was conducted, there is a 98.8% correlation between refractometer values and the total protein percentage in the samples (Majarín et al., 2018); henceforth, refractometry data will be referred to as plasma protein (%).

2.4. Statistical analysis

Data were analysed using IBM SPSS 20.0 (Amarok, NY USA) using linear mixed models. The models included the random terms replicate (1–4) and farrowing location (Room 1–5), and the main fixed effect of treatment (oxytocin, carbetocin and control). Litter size and parity were fit as covariates. All normal data were analysed using a general linear mixed model, binomial data analysed using a generalised linear mixed model with binomial distribution, and count data as a generalised linear mixed model with poisson distribution. The sow was considered the statistical unit for all measures. Piglet, therefore, was considered the repeated term for analysing cord lactate and plasma protein concentrations. In addition to the random terms, covariate and fixed effects as previously described in this manuscript, these analyses also considered the fixed effects of birth order (one-three; early, and eight to ten; late), litter size (≤10; small, 11–12; medium and > 12 large) and all interactions were fit, but only main effects were significant and retained in the final model. Data are tabulated as least squares means ± the standard error of the mean. Pairwise comparisons were conducted using the LSD *post hoc* test when $P < 0.05$.

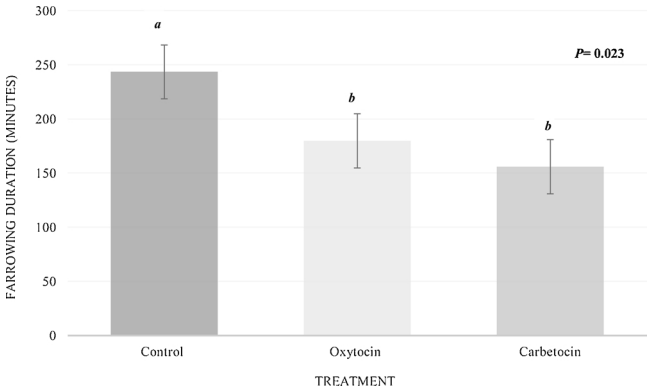

Fig. 1. Farrowing duration (min) of sows treated with either a single dose of oxytocin or carbetocin immediately after the birth of the first piglet, or no treatment. Farrowing duration was defined as the interval between delivery of the first and last piglet.

3. Results

3.1. Sow performance

Treatment had an effect on the duration of farrowing, with carbetocin and oxytocin treated sows farrowing in a shorter time interval than sows of the control group ($P = 0.023$; Fig. 1.). On average, the duration of farrowing was 87 min shorter in carbetocin-treated sows and 64 min shorter for oxytocin treated sows as compared with the sows of the control group (Table 1). There was no significant difference for average farrowing duration between oxytocin- and carbetocin-treated sows. No significant differences were observed between mean number of dystocia events ($P = 0.338$), or number of stillbirths per litter ($P = 0.233$; Table 1). Parity was evenly distributed across treatments as was total piglets born alive in the litter ($P = 0.84$; Table 1).

3.2. Piglet performance

Birth order affected piglet cord lactate concentration ($P = 0.001$; Table 2), with piglets born later in the birth order having greater concentrations. Birth order also affected plasma protein concentrations, with those born early in the birth order having greater concentrations than those born later ($P = 0.005$; Table 2).

3.2.1. Lactate concentration of piglet cord blood

Umbilical cord lactate concentration was greater in sows of the oxytocin-treated and control groups when compared with the carbetocin group ($P = 0.008$; Fig. 2.). The average blood lactate concentration of piglets from sows in the control and oxytocin groups was not different (Fig. 2; Table 2).

3.2.2. Plasma protein (%) in piglets 24 h after birth

Piglets from carbetocin-treated sows had lesser protein concentration in their blood than piglets from oxytocin-treated or control sows ($P = 0.001$; Fig. 3.). Piglets from oxytocin-treated and control sows had similar protein concentrations in their blood (Fig.3; Table 2).

4. Discussion

Compared to controls, carbetocin was effective as a uterotonic agent by reducing farrowing duration by more than 1 h. There have been few investigations where there was examination of the effectiveness of carbetocin on sow farrowing duration, although results from a recent study are inconsistent with those from the present study (Boonraungrod et al., 2018). Experimental design differences

Table 1
Treatment (control, oxytocin and carbetocin) effects (means ± SEM) on farrowing assistance (dystocia) and sow performance (litter size and stillbirth).

	Control	Oxytocin	Carbetocin	*P*-value
Parity	2.7 ± 0.5	2.3 ± 0.5	2.4 ± 0.5	0.84
Farrowing duration	243.5^{a} ± 26.1	179.8^{b} ± 25.2	155.9^{b} ± 25.2	0.023
Mean dystocia events	1 ± 0.2	1.1 ± 0.2	0.8 ± 0.2	0.338
Number of stillbirths per litter	0.7 ± 0.2	0.5 ± 0.1	0.7 ± 2	0.223
Piglets born alive	12.5 ± 0.4	12.4 ± 0.4	12.6 ± 0.4	0.87

Table 2
Effect of treatment, piglet birth order and litter size on umbilical cord lactate concentrations and piglet plasma protein percent at 24 h post-partum (means ± SEM).

	Cord lactate (nmol/l)	*P-value*	Plasma protein (%)	*P*-value
Treatment		0.008		0.005
Control	54.5 ^{a} ± 1.9		5.8^{a} ± 0.1	
Oxytocin	54.6 ^{a} ± 1.9		5.8^{a} ± 0.1	
Carbetocin	50.0 ^{b} ± 1.7		5.2^{b} ± 0.1	
Birth order		0.001		0.005
Early (1-3)	45.4 ^{a} ± 2.4		5.7 ^{a} ± 0.1	
Late (8-10)	56.6 ^{b} ± 2.2		5.4 ^{b} ± 0.1	
Litter size		0.018		0.667
Small (< 10 piglets)	47.3^{b} ± 4.6		5.6 ± 0.2	
Medium (10-12 piglets)	54.7^{a} ± 1.7		5.5 ± 0.2	
Large (> 12 piglets)	51.12^{b} ± 1.8		5.3 ± 0.1	

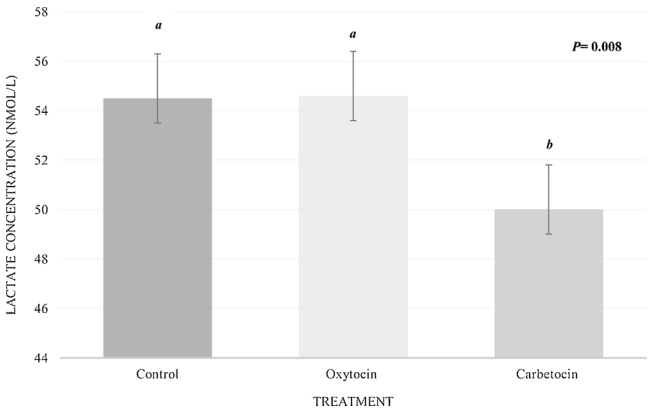

Fig. 2. Umbilical cord blood lactate concentrations (nmol/L) of piglets from sows in the oxytocin, carbetocin and control treatment groups immediately after birth.

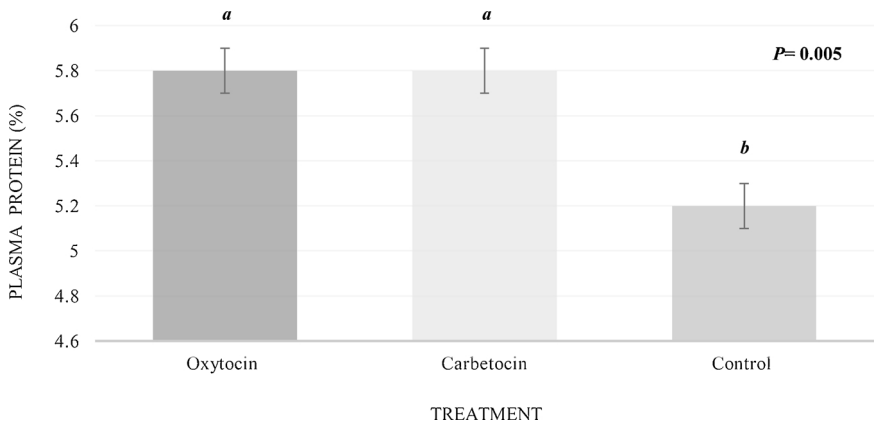

Fig. 3. Percent plasma protein of piglets 24 h after birth from sows in the oxytocin, carbetocin and control treatment groups.

exist, however, between the previous and the current study. Boonraungrod et al. (2018) administered the carbetocin as part of an induction protocol prior to the onset of farrowing which probably contributed to the marked incidence of dystocia. The aim of this previous study was to induce sows to farrow within the timeframe during the day when there were personnel present to observe farrowings. In the present study, carbetocin was administered during the period when farrowing was occurring to assist in the farrowing process with the aim of improving piglet viability. Thus, the inconsistent results between the present and previous study are not unexpected. When results from previous and present studies are considered collectively, carbetocin appears to be an acceptable alternative to oxytocin with regards to both facilitating farrowing induction and decreasing the duration of the farrowing period.

There were no treatment effects on the incidence of dystocia in the present study. Results of earlier research indicated a dose

dependant association between oxytocin treatment and the need for manual intervention during farrowing (Welp et al., 1984). The absence of adverse effects in the present study may be due to the use of a relatively smaller dose of oxytocin (10 IU) combined with it being administered after the delivery of the first piglet. Because there was no increased need for farrowing assistance in the oxytocin-treated group in the present study as compared with the control group, the expected positive effect of carbetocin on incidence of dystocia could not beascertained.

The uterotonic effect of carbetocin in the present study was not different to that of oxytocin with regards to farrowing duration and need for manual assistance during farrowing. Results of previous studies indicate oxytocin administration before delivery of the first piglet resulted in longer farrowing durations and increased numbers of stillbirth piglets (Kirkwood and Thacker, 1995). When oxytocin was administered after one piglet was born, the overall duration of farrowing was reduced, although number of stillbirth piglets were similar when oxytocin was administered before or after the birth of the first piglet (Mota-Rojas et al., 2002).

In the current study, piglets from carbetocin-treated sows had the least cord blood lactate concentration compared with oxytocin-treated and control sows. With relatively greater concentrations of cord blood lactate being an indicator of hypoxia during parturition (Kraut and Madais, 2014), this finding indicates carbetocin treatment had a significant uterotonic effect without there being a compromising of uterine blood flow. Presumably, the absence of adequate myometrial tone, which may occur in sows as a result of successive parities was responsible for the relatively greater cord blood lactate in sows of the control group as compared to what was expected.

A relatively lesser uterine tone prolongs the time of parturition for the entire litter, thus extending both farrowing duration and incidence of piglet hypoxia. As for oxytocin-treated sows, there would be piglet transport to the cranial cervical area without enough myometrial contractile force occurring to propel the foetus through the cervical lumen leading to an accumulation of piglets in the caudal uterine area resulting in anoxia conditions for the piglets. Even when there has not been compromising of a sow's uterine tone as a result of multiple parities, the uterine contractions induced by oxytocin can be marked to the extent there is traumatising of the foetus or rupture umbilical cords and an increase in the incidence of piglet hypoxia.

The differential effect that occurred when there was treatment oxytocin as compared to carbetocin is perhaps further evidence that perinatal oxytocin treatment frequently results in an increased piglet meconium staining suggestive of intrapartum hypoxia (Mota-Rojas et al., 2002; Alonso-Spilsbury et al., 2004; Kirkden et al., 2013). The results of the present study indicate that there should not be use of oxytocin in sows that are farrowing because of the risks of piglet hypoxia. Consistent with this recommendation with regards to stillbirths, treatment with carbetocin consistently resulted in the lesser piglet cord lactate concentrations and, therefore, there should be further investigation of this compound as a possible alternate farrowing aid.

It was hypothesised in the present study that compromised uterine blood flow in oxytocin-treated sows would reduce piglet vitality, and this would not occur following carbetocin treatment of sows. Even temporary hypoxia can cause permanent damage to the central nervous system of piglets, which may disrupt normal suckling instincts (Mota-Rojas et al., 2005b). Colostrum is rich source of immunoglobulins, thus total protein in plasma was measured in piglets to estimate colostrum intake as an indicator of piglet vitality. While piglets from carbetocin- as compared with oxytocin treated sows did have lesser blood lactate concentrations, the plasma protein concentrations were consistently less. The immunoglobulin content in sow colostrum is highly variable (Declerck et al., 2015), and this may have been a confounding factor in using protein in piglet plasma as an indicator of pig vitality in the present study.

Another possible reason protein concentrations were less with carbetocin treatment could be the piglet's capacity to transfer protein from its gut to the bloodstream. Bland et al. (2003) reported there was a substantial variability between piglets in the capacity to transfer immunoglobulins from the gut to the bloodstream. Even though piglets may have ingested a large amount of colostrum post-partum, it is the capacity to transport immunoglobulins across the intestinal wall that determines how much of the immunoglobulins enters into the blood. Pacha (2000) reported that immunoglobulins in colostrum are transported from the gut lumen into the blood through specific and non-specific pathways, however, there was not assessments in the present study about how or if sow treatments affected transport of molecules across the gut wall.

Taken together, blood protein content in isolation is likely a poor indicator of colostrum intake and consequently piglet vitality, therefore, piglet weight gain during the period of colostrum production would likely be a more reliable indicator of pig viability. Boonraungrod et al. (2018) reported that there was similar colostrum intake, as measured by 24 h weight gain, of piglets from carbetocin-treated and control sows, which is consistent with the results of the present study for total plasma protein concentrations. There was speculation as a result of results from this previous study that there was reduced immunoglobulin absorption due to reduced milk intake. This line of thought existed because of the reports of Mota-Rojas et al. (2005a) in which it was suggested that increased foetal hypoxia during parturition was responsible for reduced piglet colostrum intake. The results of the current study are not consistent with this line of thought (the least concentrations of cord lactate were observed with the carbetocin treatment), and so further research should be conducted to identify whether there are any sow factors that explain this difference in either piglet colostrum intake or the transmural transport of macromolecules.

In conclusion, carbetocin administered after the birth of the first piglet reduced farrowing duration, resulted in the least incidence of stillborn piglets and reduced liveborn cord lactate concentrations across parities. These findings indicate carbetocin is a preferred alternative to oxytocin when administered near the time of initiation of farrowing. The reduction in total plasma protein concentrations in piglets from carbetocin-treated sows is concerning, and future research examining the underpinning mechanisms of a potentially reduced sow colostrum output is required before carbetocin can be included as part of a farrowing management regimen for sows.

Conflicts of interest

None

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