

Primary uterine inertia in 27 bitches: aetiology and treatment

OBJECTIVES: To evaluate two treatment methods in bitches with primary uterine inertia in relation to blood concentrations of oxytocin, calcium and glucose.

METHODS: A prospective study where 27 bitches with primary inertia were randomly allocated to treatment groups I and II. Blood samples were collected before and after treatment. Group I was treated with a combination of intravenous calcium solutions and oxytocin and group II with oxytocin only. If unsuccessful, caesarean sections or additional medical treatment was pursued.

RESULTS: Plasma oxytocin concentrations were 35 ± 15 pmol/l in group I and 30 ± 15 pmol/l in group II. Before treatment, the total serum calcium concentrations were 2.1 ± 0.2 mmol/l in both the groups, and blood glucose values were 7.0 ± 0.5 mmol/l (group I) and 7.3 ± 1.4 mmol/l (group II). The number of bitches subjected to caesarean sections and the number of puppies born did not differ between the two groups.

CLINICAL SIGNIFICANCE: This study indicates that low plasma oxytocin levels is a cause of primary inertia in bitches with normal serum calcium concentrations and aggravates the condition in bitches with low calcium levels. Hypoglycaemia was not observed. The outcome of labour did not differ between groups I and II.

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INTRODUCTION

Dystocia is defined as the inability to expel fetuses through the birth canal and occurs in about 5 per cent of all parturitions in dogs (Linde-Forsberg and Eneroth 2000). The cause may be maternal or fetal. The most common form in bitches is primary inertia which can be classified as complete or partial (van den Weijden and Taverne 1994). In complete primary inertia, the bitch does not start labour. In partial primary inertia, the bitch may start to deliver her puppies, but the labour ends prematurely, despite the presence of a patent birth canal.

Oxytocin and prostaglandins are important for effective myometrial contractions (Guyton and Hall 2000). The number and activity of the oxytocin recep-

tors in the myometrium increase during late pregnancy, and maximal levels are reached during onset of labour in human beings and cattle (Fuchs and others 1984, 1992). In female dogs, a rise in plasma oxytocin secretion coincides with the first labour contractions (Olsson and others 2003).

In addition to hormonal influences, the myometrium needs calcium ions to contract. There is evidence that serum calcium concentration in bitches with primary inertia is similar to that in those with normal myometrial contractions (Kraus and Schwab 1990), but it is not known if a low intracellular calcium content is the cause of the weak myometrial contractions. Furthermore, it has been proposed that hypoglycaemia is a cause of primary inertia, especially in small breeds of dogs (Linde-Forsberg and Eneroth 2000).

Bitches with primary inertia are subjected to different treatments. The veterinarian often initially treats the bitches medically, but if the response is incomplete, a caesarean section (CS) is recommended. Unlike in many other countries, Swedish veterinarians commonly give intravenous (iv) infusions of calcium solutions initially, which is supplemented with oxytocin injections if needed. If the dog is hypoglycaemic, glucose solutions are given intravenously. The iv crystalloid solutions are administered to correct fluid, electrolyte and acid-base imbalances.

The purposes of this study were to investigate if bitches with primary uterine inertia have low concentrations of oxytocin, calcium and glucose in the blood, and to evaluate the outcome of two medical treatments, one with calcium infusion, followed by oxytocin injection and the other with oxytocin injections only.

MATERIALS AND METHODS

Animals

The Local Ethical Committee in Uppsala and the Swedish Board of Agriculture approved the experimental design. Bitches that were presented to the Department of

Small Animal Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden, and diagnosed with primary inertia were included in the study. All owners were informed, and they gave their consent before the dogs were included in the study. Primary uterine inertia was diagnosed based on clinical signs consistent with first- or second-stage of labour and with no signs of secondary uterine inertia. Also, bitches with primary complete uterine inertia that could not begin labour at full term were included.

Physical examination and digital vaginal palpation in combination with diagnostic imaging were used to confirm the diagnosis. Radiographs were used to count the number of puppies and to observe signs of fetal malposition or, in some cases, fetal death. The ultrasound made it possible to count the heartbeats of the fetuses. The bitches were excluded from the study and subjected to CS if there were signs of slow (<150 bpm) or no fetal heartbeats and of fetal malposition.

Bitches in first-stage labour had no born puppies and no allantois visible. They showed signs of panting, nesting, shivering and often a temperature decrease that exceeded the normal time frame for first-stage labour. Bitches in second-stage labour had a history of visible but weak abdominal contractions and the puppies might have been delivered or the allantois might have burst.

Oxytocin analysis was also performed on blood samples that had been taken from seven healthy beagle bitches born and housed at the Department of Small Animal Clinical Sciences.

Medical treatment

Two treatment methods were used at random and, if necessary, each treatment was administered twice. Method I consisted of an iv infusion of 1 ml/kg (maximum 20 ml) calcium glubionate (Calcium-Sandoz, 9 mg Ca/ml; Novartis) in 80 ml of 0.15 M sodium chloride, followed by 0.2 ml iv oxytocin (Partoxin vet, 10 iu/ml; Pharmaxim) after 30 to 60 minutes. Method II consisted of an iv infusion of 0.2 ml oxytocin (Partoxin vet, 10 iu/ml; Pharmaxim) repeated once after 30 to 60 minutes. In addition, all bitches were given iv fluid

therapy (Rehydrex with 25 mg/ml glucose; Fresenius Kabi) during and between the treatments.

If the bitches still had puppies left after completion of two medical treatments, a CS was performed or additional medical treatments were administered, but no further blood samples were taken. In group I, one bitch was treated with an additional injection of oxytocin and then finished whelping. All the other bitches underwent CS (Table 1). In group II, two bitches were treated with one additional injection of oxytocin each and a third bitch got an infusion of calcium intravenously. All of them delivered their puppies. The other bitches in that group underwent CS (Table 1). The decision was made at the discretion of the clinician treating the case.

Collection of blood samples

An iv catheter was inserted into the cephalic vein and the blood samples were collected into two 4 ml K₃-ethylenediaminetetraacetic acid (EDTA) tubes and one 5 ml serum tube. In addition, blood samples for analysis of oxytocin were taken by venipuncture into K₃-EDTA tubes from seven non-pregnant beagle bitches kept at the authors department. Medical treatments started immediately after obtaining the pretreatment blood samples. After completion of the treatments, a new blood sample was taken into a serum tube.

Analyses of blood samples

Total serum calcium was analysed before and after treatment and serum albumin before treatment. The variables were analysed by the Department of Clinical Pathology, Swedish University of Agricultural Sciences, using routine laboratory methods. Whole-blood glucose concentration was analysed by reflectance photometry (Reflotron; Boehringer Mannheim).

Serum calcium concentrations were corrected for hypoalbuminaemia using the formula:

$$\begin{aligned} \text{Calcium (mmol/l)} / 0.25 - \text{Albumin (g/l)} / \\ 10 + 3.5 = \text{Corrected calcium (mg/dl)} \\ \times 0.25 = \text{Corrected calcium (mmol/l)} \end{aligned}$$

The plasma oxytocin concentration was determined in principle as described by

Stock and Uvnäs-Moberg (1988) but modified and validated for canine plasma. Dilutions of the canine plasma were parallel to the standard curve of the radioimmunoassay used. Before the analysis of oxytocin, plasma was extracted using acetone (GR, Merck) and petroleum benzene (GR, boiling range 40 to 60°C; Merck), with a recovery rate of 81 per cent. The rabbit antiserum XS 3014 (Eurodiagnostica AB) was diluted 1:28,000 in the incubation phosphate buffer (pH 7.6) with 0.005 per cent Tween 80. Bound and free ligands were separated by adding 1 ml of decanting suspension (sheep anti-rabbit, No. 3; Pharmacia & Upjohn Diagnostics). The lower detection limit was 1.7 pmol/l and the intra-assay coefficient of variance was <10 per cent.

Statistical analyses

The statistical analyses were performed by the program JMP 5.1. Statistical methods used included student's *t* tests for continuous data and Fischer's exact two-tailed test for nominal data. Minimal level for significance was set at *P*<0.05. Descriptive statistical data are reported as mean (sd).

RESULTS

In total, 27 bitches were included in the study. Nineteen breeds and two mixed-breed dogs were represented by at least one case each, and four breeds had more cases: cavalier King Charles spaniel (*n*=3), boxer (*n*=3), English springer spaniel (*n*=2) and Labrador retriever (*n*=2). The latter breeds were as evenly distributed as possible into the two treatment groups (Table 1).

In group I, the bitches were 5.4 (1.3) years old, and in group II, they were 4.2 (1.4) years old (*P*=0.98).

Before treatment, the plasma oxytocin concentration was significantly higher both in groups I and II compared with that in the non-pregnant bitches (*P*=0.006) (Table 2).

Before treatment, seven bitches in group I and five in group II had total serum calcium values below the reference value (Table 2). The calcium concentrations did not differ before and after treatment within group I (*P*=0.92) or group II (*P*=0.07).

Table 1. Birth outcome with breed presentation. Number of puppies born before and after medical treatment in bitches with primary uterine inertia. Puppies not delivered during the study are presented and also how they were treated

Id number	Breed	P born before T	T No. I*,†	T No. II*,†	Stillborn P during medical treatment	P not delivered during medical treatment	Treatment after study
Medical treatment group I							
1	Dachshund	6	2/0	F		0	F
2	English springer spaniel	6	0/1	0/4	1	1	‡
3	Clumber spaniel	0	0	0		3	CS
4	CKCS	0	0/1	0		5	CS
5	Mittel pinscher	0	C			3	CS
6	Danish/Swedish farmdog	1	3/2	1/0	1	1	Oxy
7	Rhodesian ridgeback	0	0	C		8	CS
8	Shetland sheepdog	0	3/1	2/0		F	F
9	Boxer	2	0	C		2	CS
10	Mixed breed	2	1/0	C		3	CS
11	Beagle	2	1/2	F		0	F
12	Boxer	2	0	C		2	CS
13	Papillon	0	C			4	CS
14	Mixed breed	0	0/1	1/0		1	CS
Total		21	18	8	2	33	
Medical treatment group II							
15	Chihuahua shorthair	0	0	C		1	CS
16	English springer spaniel	6	1	1	1	F	F
17	Shih-tzu	2	2	1		2	CS
18	Dandie Dinmont terrier	0	3	1		F	F
19	CKCS	1	0	0		3	CS
20	Boston terrier	0	0	C		3	CS
21	CKCS	2	0	2		1	Oxy
22	Basset Fauve de Bretagne	0	0	1		1	Ca
23	Labrador retriever	0	2	F		0	F
24	Boxer	2	0	0		1	CS
25	Drever (Swedish hunting dog)	6	1	1		1	Oxy
26	Labrador retriever	0	1	0		5	CS
27	Dobermann	0	0	0		2	CS
Total		19	10	7	1	20	

P Puppies, C Cancelling treatment, F Finished labour, CS Caesarean section, Oxy Oxytocin, Ca Calcium, CKCS Cavalier King Charles spaniel, T Treatment

*Includes dead born puppies

†Before slash: puppies born after calcium infusion only; after slash: puppies born after calcium infusion, followed by oxytocin injection

‡No further medical or surgical treatment needed

The albumin concentration was low in five of the seven bitches with decreased total calcium concentrations in group I and three of the five bitches in group II before treatment (Table 2).

The calcium concentrations in five of the 12 hypocalcaemic animals were within the reference range when corrected for hypoalbuminaemia.

For technical reasons, glucose could not be analysed in all the dogs. However, in this study, the glucose concentration was at or above the upper reference value before treatment. After treatment, it had increased in both groups ($P=0.008$) (Table 2).

Effects of treatment

Group I In treatment group I, seven bitches had delivered 21 puppies before treatment started. In response to the planned medical treatment, they gave

birth to 17 more puppies, but 26 puppies remained (Table 1). The other seven dams in this group had not delivered any puppy before treatment, but nine of 33 puppies were delivered after the two treatments. The difference between these bitches was significant ($P=0.004$).

Ten puppies were born after the first calcium infusion and eight more after the oxytocin injection. Two of the bitches (14 per cent) had successfully delivered all their puppies after the first treatment. Four puppies were born after the second calcium infusion and four (from the same bitch) after the second oxytocin infusion. After the second treatment, one dam (8 per cent) had finished labour (Table 1).

In six dams (43 per cent), the treatments were interrupted prematurely due to insufficient response (no born puppies) to the medical treatment and they were subjected to CS (Table 1). After the two

treatments were finished, five bitches (36 per cent) still had puppies left in the uterus and were either given additional medical treatment or subjected to CS but were not followed with more blood samples. Two puppies were stillborn during the medical treatment (Table 1).

Twenty-six of 59 puppies were born during the medical treatment in this study and in total, 64 per cent of the dams were subjected to CS in group I.

Group II In treatment group II, six bitches had delivered 19 puppies before treatment started (Table 1). The number of puppies born during treatment did not differ whether the bitches had or had not delivered before treatment ($P=0.51$). The number of puppies born after the first injection of oxytocin was 10 and seven after the second injection. After the first treatment, one bitch (8 per cent) had finished labour. After the second treatment,

Table 2. Blood concentrations of oxytocin, total calcium, albumin and glucose in bitches with primary uterine inertia*

Parameter	Treatment group I	Treatment group II	P value	Reference range
Oxytocin (pmol/l)				
Pretreatment	35 (15) (n=11)	30 (15) (n=11)	P=0.79	Non-pregnant bitches: 17 (4) (n=7); normal bitches in labour: 166 (19) (n=5)†
Range	16-63	19-73		
Total calcium (mmol/l)				
Pretreatment	2.1 (0.2) (n=14)	2.1 (0.2) (n=13)	P=0.44	2.2-2.9
Range	1.8-2.4	1.8-2.4		
After treatment	2.3 (0.3) (n=9)	2.0 (0.2) (n=10)	P=0.96	2.2-2.9
Range	2.0-3.0	1.7-2.4		
Albumin (g/l)	29 (3) (n=13)	29 (3) (n=13)	P=0.31	28-37
Range	24-33	24-35		
Glucose (mmol/l)				
Pretreatment	7.0 (0.5) (n=10)	7.3 (1.4) (n=7)	P=0.25	4.1-7.0
Range	6.5-7.9	5.2-9.0		
After treatment	7.9 (1.1) (n=8)	7.9 (0.7) (n=5)	P=0.52	4.1-7.0
Range	6.7-9.9	6.9-8.6		

*With the exception from the oxytocin values, the reference ranges are for non-pregnant dogs

†Olsson and others (2003)

two more dams (17 per cent) had finished labour.

In two other dams (15 per cent), the treatments were interrupted prematurely due to insufficient response to the first oxytocin injection and they were subjected to CS (Table 1). After the two treatments were completed, eight bitches (61 per cent) still had puppies left in the uterus and were either treated medically again or subjected to CS but were not followed with more blood samples. One puppy was stillborn during the medical treatment.

In group II, 17 of 37 puppies were delivered during the medical treatment included in the study. This outcome did not differ significantly from group I ($P=1.00$).

Despite the medical treatments, 54 per cent of the dams in group II were subjected to CS. This outcome did not differ significantly from group I ($P=0.70$).

DISCUSSION

Ferguson's reflex is normally activated by the fetus in the birth canal (Ferguson 1941), which stimulates the release of oxytocin, causing effective uterine contractions. In the 27 bitches diagnosed here with primary uterine inertia, plasma oxytocin concentration was significantly lower compared with the 3.3 times higher values observed during normal labour in bitches in a previous study using the very

same analysis assay as in the present study (Olsson and others 2003). The low oxytocin concentration may have been the cause of inertia in the bitches that started to deliver puppies after injection of oxytocin. However, 30 per cent of the dogs did not respond to oxytocin treatment. These may have had a defect in or a down-regulation of the oxytocin receptor function in the myometrium. To the authors' knowledge, no studies of canine myometrial oxytocin receptor function have been reported. In human beings and cattle, elevated oxytocin receptor concentrations are seen during labour (Fuchs and others 1984, 1992). However, mice lacking oxytocin are fertile and can deliver their offspring (Nishimori and others 1996), so other explanations not related to oxytocin may be possible. One possibility is deficient prostaglandin $F_{2\alpha}$ synthesis or lack of effect of that substance, since it is well known that it is important for normal outcome of labour in many species. The prostaglandin $F_{2\alpha}$ metabolite starts to increase before labour in the dog and rises to very high levels during labour (Veronesi and others 2002, Olsson and others 2003), but unfortunately, it was not analysed in the present study.

Oxytocin mobilises intracellular stores of calcium and causes influx of extracellular calcium into human myometrial cells in vitro (Thornton and others 1992, Rezapour and others 1996). This shows the important interaction between oxyto-

cin and calcium during parturition and could explain why more puppies were delivered when oxytocin was given after the calcium solution.

Hypocalcaemia has been reported to be rare in uterine inertia (Gaudet 1985, Kraus and Schwab 1990), but the calcium concentrations were below normal range for non-pregnant animals in seven bitches in group I and five in group II. Three bitches in group I started to deliver when the calcium solution was given and two more when oxytocin was also administered. Two bitches did not respond and were subjected to CS. In the seven bitches with normal serum calcium concentration, three dams started to deliver during treatment, while the other four were subjected to CS. The importance of the serum calcium levels therefore remains unsettled.

One of the treatment regimens recommended for primary uterine inertia is administering glucose intravenously (Linde-Forsberg and Eneroth 2000), but in the present study, most dogs had hyperglycaemia. This could be secondary to high cortisol values, which have been observed during normal labour in dogs (Olsson and others 2003). Cortisol could not be analysed here due to insufficient amounts of plasma. However, since dystocia can be considered a stressful situation, it is suggested that cortisol values were even higher in the bitches affected by dystocia. Some support for this is the observation that the glucose concentrations

became further elevated after the medical treatment.

There were no significant differences between the two treatment groups, considering the number of born puppies and the number of stillborn puppies. In 59 per cent of the cases, the dogs were subjected to CS despite medical treatment, which corresponds with earlier reports (Darvelid and Linde-Forsberg 1994).

It is concluded that plasma oxytocin concentrations in the bitches in the present study were low compared with those in bitches during normal labour. There was no clear difference, neither in born puppies nor in the number of bitches subjected to CS, whether the bitches were treated with a combination of calcium and oxytocin or only oxytocin.

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