The use of intranasal oxytocin therapy for bitches post caesarean section

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Issues of poor maternal bonding in the bitch are commonplace in small animal theriogenology practices. Whilst any new mother can have issues accepting their newborn puppies, the problem presents itself most commonly in nulliparous bitches, more so those that have undergone caesarean section and more so those that have undergone elective caesarean section (observed, unpublished data). Whilst prolactin levels rise in late dioestrus, there is a marked rise subsequent to the progesterone decline from luteolysis induced by a rise in ACTH from the foetuses. Thus, there is a delayed rise in prolactin in bitches undergoing elective caesarean due to the procedure being undertaken before luteolysis has begun. Some breeds appear to have more of a problem accepting puppies and not uncommonly will savage their puppies, notably American Pit Bull Terriers, American Staffordshire Terriers, Rottweilers and German Shepherds (observed, unpublished data). Dealing with a bitch that is not accepting her puppies and trying to harm them is a difficult situation for both the veterinarian and the breeder; suggested treatments are limited and often lead to frustration, poor compliance and detrimental neonatal care.

Traditional therapies:
Traditionally breeders would be recommended to sedate affected bitches, use muzzles and physical restraint whilst an assistant would place the puppies on the mammary glands to try and feed. The most commonly used sedatives are diazepam (0.5 mg/kg bid-tid PO) or acetylpromazine (1-3 mg/kg bid PO). Diazepam, a benzodiazepine, whilst being a good anxiolytic agent, is poorly sedative, coupled with potential ante grade amnesia (inability to create memories after an amnesia effect) which may mean that when used to treat maternal aggression, the bitch may in fact not learn to accept the puppies as she is less likely to remember the feeding event clearly. Acetylpromazine (ACP), a phenothiazine derivative, when used orally has a good sedative effect, and through stimulation of prolactin will improve milk production (like metoclopramide). ACP can have profound side effects including seizures (by reducing the seizure threshold), profound hypotension and should be used in caution in breeds known to carry the mutated Multidrug Resistant 1 (MDR1) gene mdr1-1Δ (notably Australian Shepherds, Border Collies, Collies, White Swiss Shepherds, German Shepherds, Old English Sheepdogs and Sighthounds). Animals homozygous for the mdr1-1Δ gene have increased susceptibility to many drugs including ivermectin, moxidectin, milbemycin oxime, digoxin, opioids, ACP, vincristine and other chemotherapeutics [1]. Whilst ACP can result in profound sedation, its use to combat mismothering must be questioned. Any medication given to a nursing mother will pass on to the puppies and additionally there is little positive encouragement of the bitch to accept the puppies; merely hoping she will eventually accept them.

Muzzling and physical restraint of the bitch is questionable as a long term therapy to aid in mothering is difficult. Not only does it require multiple assistants to feed the puppies every 2-6 hours, it would be thought to be very stressful for the bitch. The increased anxiety and cortisol level associated with this would be expected to have detrimental effects on both milk let down and milk production. Whilst in some cases it may be necessary in the short term, this is not a long term therapy.

Many breeders will often resort to supplementary feeding in cases wherein nursing is difficult or not possible. This itself, whilst adequate, is not ideal for the puppies. There are many

supplementary milk's for puppies sold on the market. Most are poorly correlated to bitches milk. Many breeders create their own formula's, or follow those of their forefathers, most of which are in no way correlated to bitch milk. Handfeeding can create problems of overfeeding, underfeeding, diarrhoea or nutritional deficiencies whilst creating more work for the breeder.

Emerging therapies:
The causative agents of maternal bonding have been long shown to be oxytocin [2-6] and prolactin. The effects of oxytocin on maternal bonding has been investigated in rats, voles and sheep. Extrapolations have been made to humans and studies investigating oxytocin levels related to post-natal depression in new mothers can be found in the literature [2, 7].

Oxytocin is a neuropeptide consisting of 9 amino acids [8] and synthesized in the paraventricular and supraoptic nuclei [6]. Synthesized oxytocin is transported and stored in the posterior pituitary, or via specific projections from the paraventricular nucleus transported to other structures in the brain including the amyglada, hypothalamus and hippocampus [6]. Oxytocin is well known for its functions on milk let down and uterine contraction subsequent to release from the posterior pituitary. Oxytocin receptors are found throughout many tissues of the body, not just the uterus and mammary gland, including but not limited to the heart, liver and brain. Oxytocin receptors are a G-coupled protein receptor. Binding of oxytocin to the G-coupled protein receptor leads to a G-qα coupling leading to an increase in intracellular calcium concentration which leads to muscle contractions (this is important for uterine tissue and mammary tissue related to milk let down). When oxytocin receptors are located on neurons this will lead to release or inhibition of other hormonal neurotransmitters and modulators like serotonin, endogenous opioids and corticotrophin-releasing factor [2].

Oxytocin has a number of believed functions other than uterine contraction and milk let down. These include, but are not limited to love and pair bonding, sexual behaviour, maternal bonding, increasing trust, pro-social behaviours and reduction in anxiety [6, 9]. A syndrome in humans, Williams syndrome is characterised by increased trust, increased chance of approaching strangers, reduced social fear and love of music. The syndrome is characterised by the deletion of 28 genes, and affected individuals have been shown to have significantly higher levels of oxytocin in their plasma; aiding to indicate the important behavioural effects of oxytocin [10]. In rats it has been shown that increased intracerebral levels of oxytocin and prolactin which occur subsequent to lactating reduces the effectiveness of the HPA and reduces cortisol levels when subsequently exposed to a stressful stimuli. This has also been shown in humans indirectly wherein mothers breastfed their babies then were subsequently exposed to a stressful experience; those mothers that breastfed first had lower cortisol levels suggesting in humans too that the HPA is desensitised by oxytocin and prolactin [11].

The release of oxytocin both peripherally and centrally has been shown to occur in response to labour, parturition, lactation and vaginocervical stimulation in sheep [12] via multisynaptic neural pathways [13]. Other stimuli for central oxytocin release includes emotional stress, social interaction and sexual activity/mating [11]. Increased oestrogen and reducing progesterone of late pregnancy not only stimulates an increase in prolactin, but stimulates an increase in oxytocin receptor expression +/- sensitivity of brain sites [13]. Subsequently, with stimulation of central oxytocin release from the paraventricular nucleus and up regulation of central oxytocin receptors, there is a positive effect on recognition of offspring odour, increased attractive perception of offspring odour, mobilisation of active components of maternal behaviour, reduced maternal aggression, decreased anxiety and fear and acquisition of maternal memory [11].

Results on oxytocin related to maternal behaviour in rats is contradictory. Whilst some reports early on showed that intracerebroventricular injection of oxytocin improved maternal

responses, subsequent work in rats with the oxytocin gene removed showed immediate maternal instincts postpartum without supplementation. This suggests in rats the effects of oxytocin may be facilitatory rather than the mainstay of maternal bonding [5]. In oestrogen primed ewes oxytocin has been shown to induce full maternal responses in non-pregnant ewes in less than 30 seconds following intracerebroventricular infusion of oxytocin [14]. Maternal experience was shown to improve responsiveness to oxytocin infusion in multiparous versus nulliparous ewes [15]. Research conducted in voles shows good evidence of oxytocin related to social behaviour and bonding. Prairie voles form long term exclusive bonding with their male counterparts following mating; this same bonding has been shown to occur following intracerebroventricular infusion of oxytocin in the female, but no effect if given to the male without mating. In the male if vasopressin is infused then the bonding will occur, showing some sex differences [5].

The intranasal infusion of many molecules have been investigated. Insulin, melanocyte stimulating hormone, vasopressin, IGF-1, neuropeptides, cytokines (erythropoietin) and carbamazepine have all been shown to cross the blood brain barrier by intranasal infusion [16]. Conversely the systemic administration of oxytocin intravenously resulted in less than 0.1% of oxytocin crossing the blood brain barrier of sheep [12]. The actual mode of transport, if any, of oxytocin into the brain subsequent to intranasal infusion is the topic of current research. Suggested routes of transport include extra neural/peri neural routes along the trigeminal or olfactory nerve pathways, lymphatic transport, intraneuronal transport or active or passive transport from vasculature [16]. There are also suggestions that intranasal administration stimulates the endogenous oxytocin system which results in both peripheral and central oxytocin secretion. Transport along the olfactory nerve is unlikely as transport speeds shown in studies are faster than the transport speed of the olfactory nerve. Endogenous activation or transport via the trigeminal or subarachnoid routes are most likely. Transport into the plasma is likely via the heavily vascularised nasal mucosa and several facial veins into the peripheral circulation. In rats it has been shown that prior administration of adrenaline intranasally before administration of neuropeptides resulted in reduced concentrations of neuropeptides into the blood without reducing CSF concentrations [17] indicating that it is traversing through vasculature.

In humans experiments have shown that intranasal infusion of oxytocin will result in peak plasma levels at 15 minutes post administration, with return to baseline by 75 minutes. In the same study, peak CSF levels occurred at 75 minutes, however peak levels in the brain are likely to be earlier than this as many samples were first taken at 75 minutes, and additionally CSF samples were collected via lumbar puncture which would delay peak levels 5-10 minutes (assuming 5mm/min CSF transport of humans) [16]. This is concurred via work in non-human primates, wherein peak CSF levels were shown to occur by 35 minutes via cervical puncture. Studies have additionally shown that higher doses will peak earlier (10 minutes, 80 IU) compared with lower doses (60 minutes, 40 IU) [18], creating questions about dose, effect and concentration gradients.

The use of oxytocin in humans shows promise for diseases associated with persistent fear, repetitive behaviour, reduced trust and avoidance of social interactions, showing promise for diseases associated with reduced oxytocin levels and altered oxytocin metabolism such as autism and schizophrenia [6]. Mah et al [3] showed that mothers diagnosed with post natal depression, then given intranasal oxytocin or a placebo then subsequently exposed to an intrusive stranger, showed greater protective behaviour of offspring than those given placebo's [3].

For two years the author has administered a dose of 10 IU of oxytocin intranasally either every 2 hours or before each feed (2-6 hours) to all nulliparous bitches post elective caesarean until good maternal behaviour is noted by the owner. The solution is compounded by a compounding pharmacist to a dilution rate of 10 IU oxytocin/0.1 mL and

administered via a human nasal spray bottle (0.1 mL/spray). The dose is extrapolated from that used in experimental studies of pigs (24 IU oxytocin intranasally) [19]. The dose frequency has been extrapolated from work in other species showing the lifespan of intranasally administered oxytocin to be at least 2 hours, and maybe up to 7 hours [3]. In total there have been 127 subjects treated with the aforementioned treatment, and it has been subjectively assessed that maternal behaviours of nulliparous mothers developed more hastily compared to those that received no treatment in the past or sedation and restraint therapy. It must be noted that this is not a controlled scientific study, and is a clinical assessment and many variables may lead to the perception of improvement due to chance. In the two years since the use of this therapy the author has not had any nulliparous bitch post elective caesarean harm a puppy. In one case a Bernese mountain dog bitch undergoing therapy began showing obsessive maternal behaviours (overstimulating and cleaning of pups) which resolved post cessation of therapy. It must be noted that the therapy is off label, experimental and still anecdotal, however from clinical experience it appears to have good promise. Currently the author and others are having good success with administration of 10 IU in alternating nostrils every 2 hours (Lopate C, personal communication) until the bitch is mothering well, usually within 12-24 hours. There is scope for a controlled clinical trial observing maternal behaviours of nulliparous bitches post elective caesarean receiving either oxytocin or a placebo intranasally.

Whilst there is no clinical or scientific study of intranasal oxytocin therapy in bitches, there is a good body of literature showing increased CSF levels of oxytocin post intranasal administration in multiple species. Additionally with studies showing reduced anxiety, fear and improved maternal behaviour related to higher CSF levels of oxytocin in multiple species, it is not clear why the same would not concur in the bitch. Whether the intranasal application of oxytocin leads to direct transit to the CSF or activation of the endogenous oxytocin is not relevant in a clinical situation as a cause and effect has been developed. The management of the nulliparous bitch post elective caesarean is a challenging case for the both the veterinarian and the breeder, and subjectively on a clinical level, the use of intranasal oxytocin shows promise for aiding in appropriate therapy to aid in the welfare of breeding bitches and their puppies.

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