ABSTRACTS

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URINARY INCONTINENCE IN SPAYED BITCHES: NEW INSIGHTS INTO THE PATHOPHYSIOLOGY AND OPTIONS FOR MEDICAL TREATMENT

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INCIDENCE OF INCONTINENCE AFTER OVARECTOMY

Urinary incontinence is the involuntary loss of urine (1). In intact bitches urinary incontinence is rare (0-1 %) (2), whereas in spayed bitches the incidence is up to 20% (3). The underlying pathophysiological mechanism is mainly an acquired insufficient closure of the urethra after spaying (4). Therefore urinary incontinence after spaying is called urethral sphincter mechanism incompetence (USMI). Within one year after spaying the urethral closure pressure is significantly reduced. Because many bitches only become incontinent years after surgery it took a long time until spaying was considered to be the cause. In one study, 83 of 412 (20%) bitches became incontinent 3 to 10 years after surgery (3).

Even 40 years ago urinary incontinence was described as a rare side effect of spaying (5). However, it took 20 years to verify the causal relationship between the removal of the ovaries and urinary incontinence (6). It is still unclear what mechanism is the trigger. Neuronal damage can most likely be disregarded, as the risk of urinary incontinence is the same in ovariectomized and ovariohysterectomized bitches and in many cases the urinary incontinence occurs years after the surgery (3).

THE ROLE OF ESTROGEN DEFICIENCY

It is generally assumed that USMI after spaying is due to an estrogen deficiency (7,8). In view of other facts it appears unlikely that estrogen deficiency alone accounts for USMI after spaying. For example, bitches treated with long acting gestagens, to suppress the sexual cycle, have no increased risk for urinary incontinence, although this treatment leads to suppressed ovarian function (9) and a serum estradiol concentration that remains at a basal level (10). In addition, the daily supplementation of estrogen only results in 61-65% of incontinent bitches becoming continent (3,11,12). Also, the plasma estrogen concentration of spayed incontinent bitches is the same (13) or slightly lower (14) than that of intact, continent bitches.

MEDICAL TREATMENT OF USMI

The medical treatment of USMI is the method of choice and should always precede a surgical therapy. The action of the used substances is aimed at increasing the urethral closure pressure.

Alpha-adrenergic drugs

In the first line alpha-adrenergic agonists are used. The effect of these sympathomimetic drugs is explained by the fact, that 50% of the urethral closure pressure is generated by the sympathetic nervous system. Alpha-adrenergic agonists improve the urethral closure pressure by stimulation of the alpha-receptors of the smooth urethral musculature (13, 15-19). The treatment with alpha-adrenergic agonists results in continence in 75% of incontinent bitches.

The alpha-receptors are divided into alpha1- and alpha2-subtypes. These receptor subtypes are distributed differently in each single effector. Alpha-1 receptors are found in many target organs of the sympathetic nervous system. With a few exceptions, alpha-2 receptors are not present in target organs of the sympathetic nervous system, but in neuronal synapses. It is now known, that the alpha-receptors at the bladder neck and proximal urethra of the bitch, which are responsible for continence, belong to the subtype 1 (20).
The side effects of alpha-adrenergic agonists is explained by the fact that alpha-1 receptors are not just found at the bladder neck, but also in other organs, especially in the wall of blood vessels. Phenylpropanolamine (PPA) acts selectively on alpha-1 receptors.

The older substance Ephedrine is less selective than PPA. It also stimulates beta-receptors and therefore has the tendency to have more side effects (15,16). In contrast to PPA a habituation to Ephedrine occurs. Because of these reasons PPA is the therapy of first choice.

In humans treatment with PPA sometimes causes side effects, such as an increase in blood pressure and headache. It may occasionally trigger a stroke or a heart attack and is therefore no longer used. When PPA was used in dogs at the recommended dose of 1.5 mg/kg BW bid or tid, an increase in blood pressure was not observed (18,21). The side effects observed in dogs were never life threatening and usually were self-limiting; diarrhea, vomiting, anorexia, apathy, nervousness and aggressiveness (3,19,22).

**Estrogens**

An alternative is the treatment with estrogens, which is successful in 65% (3,12,23). However, with estrogens unwanted side effects can occur such as swelling of the vulva and attractiveness of male dogs (12). Nowadays only short-acting estrogens (Estriol, Incurin®, Intervet, Netherlands) are used (11). The depot preparations used in the past are obsolete, in part because they can potentially cause bone marrow depression (24). Estrogens indirectly increase the urethral closure pressure; they sensitize the alpha-receptors for endogenous and exogenous catecholamines (25). If therapy with alpha-adrenergic agonists is unsatisfactory, a combination with estrogens may potentiate the effect.

**GnRH depot analogues**

As mentioned before not all the observations can be explained by estrogen deficiency as being the sole underlying cause of urinary incontinence after spaying. Also, it is not the only endocrine hormonal change after spaying. By removing the ovaries the feedback function of the gonadal hormones on the hypothalamic-pituitary system is missing (26), which in turn results in a several fold increase of the initial plasma levels of the two gonadotropins (follicle stimulating hormone FSH, and luteinizing hormone, LH) (27,28). The question arises, are the elevated FSH and LH concentrations responsible for the high incidence of urinary incontinence in spayed bitches. If this were correct then the suppression of the gonadotropin secretion would result in continence in affected bitches. GnRH depot preparations are suitable for the suppression of FSH and LH secretion. These are subcutaneously administered implants, which continuously secrete GnRH and, dependant on the preparation, result in an elevated blood concentration over weeks or months. This leads to a down-regulation of the GnRH-receptors in the pituitary and thereafter to a decrease of the FSH and LH concentrations to a low level.

Seven of thirteen bitches with USMI after spaying did indeed become continent, for an average period of 247 days (29), after receiving depot preparations of GnRH-analogues. However, it is questionable if the therapeutic success is due to a decrease of the gonadotropin concentrations as there was no difference in the concentrations for responders and non-responders (30). It is possible that the success of the treatment is not based on a decrease in the FSH and LH, but instead on a direct effect of the GnRH on the lower urinary tract. This idea is quite conceivable as recently our working group has been able for the first time to prove the presence of LH, FSH and also GnRH receptors in the bladder and urethra of bitches.
Apart from that, recent studies show that the effect of GnRH is not limited to the regulation of pituitary hormones, but GnRH is also produced outside of the hypothalamus and may have a direct effect on the target organs.

The fact that GnRH, FSH and LH receptors are expressed in the lower urinary tract and other organs supports the assumption that GnRH performs specific functions in the tissue and that a widely distributed paracrine or autocrine regulatory system exists.

In about 50% of bitches with urinary incontinence treatment with GnRH-analogues is successful. Based on the proposed pathophysiology of USMI, that after spaying the decrease in urethral closure pressure is the underlying cause for urinary incontinence, it seems reasonable to assume that the success of the therapy is a normalization of the urethral sphincter mechanism. However, this hypothesis was clearly disproved by the recording of urethral pressure profiles of incontinent bitches before and after GnRH treatment. The application of GnRH had no significant effect on the urodynamic parameters, even in successfully treated bitches. Recent studies in Beagle bitches may assume that GnRH modulates bladder function. In 10 spayed Beagle bitches cystometric examinations were performed before and after treatment with depot formulations of GnRH analogues. The results showed a doubling of the difference between the medium and maximum bladder filling volume at the same bladder pressure after GnRH treatment.

References