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Title: A CANINE URINARY DISTURBANCE MODEL IN ASSOCIATION WITH BENIGN PROSTATIC HYPERPLASIA.

Aims of Study:

Both man and dog spontaneously develop benign prostatic hyperplasia (BPH), so the dog has been used as an *in vivo* model to study BPH and to evaluate the drugs for BPH. But, in dog, it has been difficult to establish the urinary disturbance in association with BPH. Accordingly, we modified a method described by Broderick et al. [1] and developed a canine urinary disturbance model in conscious. The aim of this study was to evaluate this canine model by the administration of an anti-androgen agent and also evaluate the efficacy of a novel testosterone 5α-reductase inhibitor in this model.

Methods:

Twenty-one male beagle dogs (9 months old) were used. Under an intravenous pentobarbital anesthesia, a polyethylene catheter was inserted into bladder dome for the cystometry, and the prostate was encapsulated with a nylon mesh except the sham-operated group (n=5). After the operation, testosterone (4mg/kg) and β-estradiol (0.04mg/kg) were administered subcutaneously for 3 weeks. At the same time of steroids administration, an anti-androgen agent (chlormadinone acetate: CMA, 3.2mg/kg, Wako pure chemical) was administered orally (n=5), and a novel testosterone 5α-reductase inhibitor ((-)-(S)-4-[1-[4-[1-(4-isobutylphenyl) butoxy] benzoyl]-indolizin-3-yl] butyric acid; TF-505, 3.2mg/kg, Taiho) was administered in the same manner (n=5). Every 7 days, the micturition pressure, basal pressure, threshfold pressure, urine weight, time of urination, frequency and amplitude of spontaneously occurring changes in intravesical pressure were measured for 4 hours by the telemetry system in conscious dog. On the basis of these parameters, the micturition patterns were divided into the regular micturition, the frequent micturition and the urinary incontinence. The day after the final administration, both the prostate and bladder were excised under an intravenous pentobarbital anesthesia and weighed. Then, the prostate and bladder were fixed in 10 % neutral buffered formalin, embedded in paraffin and stained with hematoxylin and eosin.

Results:

In the sham-operated group, no urinary disturbance was observed. By the administration of steroids (BPH group, n=6), the frequent micturition and/or the urinary incontinence were induced and both the prostate and bladder weights were significantly increased in comparison with the sham-operated group. Histopathologically, the proliferartion of prostatic epithelial cells was observed in BPH group. The administration of CMA resulted in

a significant improvement of the urinary disturbance and also a marked reduction of prostate weight (8.5 ± 0.5 g) in comparison with BPH group (15.8 ± 1.2 g). In this canine model, the administration of TF-505 resulted in a significant improvement of the urinary disturbance, a significant reduction of bladder weight (10.7 ± 1.5 g) in comparison with BPH group (25.2 ± 6.3 g) and also a reduction of prostate weight.

Conclusions:

It was confirmed that the canine model with steroid-induced urinary disturbance developed the frequent micturition and/or the urinary incontinence and they will provide a useful model for the evaluation of drugs for BPH. In this model, TF-505, a novel testosterone 5α-reductase inhibitor, improved the urinary disturbance.

Reference:

[1] A novel canine model of partial outlet obstruction secondary to prostatic hypertrophy. World J Urol 1994;12: 245-248