

COMBINATION TREATMENT WITH AN ANTICHOLINERGIC AGENT AND ALPHA-BLOCKER IN A CANINE URINARY DISTURBANCE MODEL IN ASSOCIATION WITH BENIGN PROSTATIC HYPERPLASIA

Hypothesis / aims of study

Combination treatment with an anticholinergic agent and an alpha-blocker has been used for treatment of bladder outlet obstruction in patients with benign prostatic hyperplasia (BPH)[1]. However, very limited information regarding the mechanism of action and efficacy of combination therapy in BPH is available in the literature. Accordingly, we performed cystometrography in a canine model with steroid-induced urinary disturbance, and investigated the therapeutic effects of an anticholinergic agent or an alpha-blocker or both, in this study the effectiveness of combined therapy in the BPH model with the parameters of bladder function, bladder weight and histopathological changes in the bladder were evaluated.

Study design, materials and methods

To establish an animal model of urinary disturbance, we used the method of Broderick et al. [2] with some modifications in 24 male beagle dogs. Under intravenous pentobarbital anesthesia, a polyurethane catheter was inserted into the bladder dome for the cystometry, and the prostate was encapsulated with a nylon mesh, except for the sham-operated group. After the operation, testosterone (4 mg/kg) and β -estradiol (0.04 mg/kg) were administered subcutaneously for 3 weeks. Simultaneously with steroid administration, an anti-androgen (chlormadinone acetate: CMA, 3.2 mg/kg) or an anticholinergic agent (propiverine HCl: Prop, 1 mg/kg) or an alpha-blocker (tamsulosin HCl: Tam, 0.1 mg/kg) or both, were administered orally. Every 7 days, bladder function parameters (urinary frequency, voided volume and interval of micturition) were measured for 3 hours in the conscious dog. On the basis of these parameters, the micturition patterns were divided into regular micturition, frequent micturition and urinary incontinence. The day after the final administration, both the prostate and bladder were excised under an intravenous pentobarbital anesthesia and weighed.

Results

In the sham-operated group, no urinary disturbance was observed. Frequent micturition or urinary incontinence or both were induced by the administration of steroids, and both the prostate and the bladder weights significantly increased in comparison with the sham-operated group (Fig. 1, Table 1). In the histopathological examination of the bladder, the edema, muscle thickening and inflammatory cell infiltration were observed in the BPH group. The administration of CMA resulted in a significant improvement of the urinary disturbance and also reduced increase of prostate and bladder weights. The administration of Prop or Tam tended to improve the urinary disturbance, with no changes in the bladder or prostate weights. On the other hand, the co-administration of Prop and Tam resulted in a significant improvement of the urinary disturbance, and reduction of bladder weight but prostate weight was not changed. The bladder histopathological finding score decreased in the following order: Normal control < Prop + Tam < CMA < Tam < Prop < BPH control.

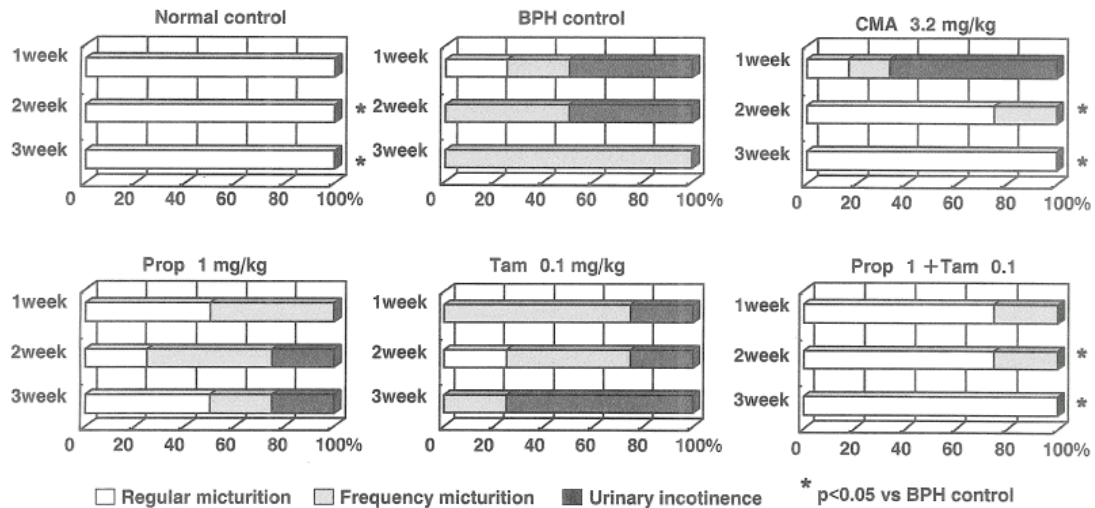


Fig. 1 Effect of drugs on the conversion of symptom in the partial outlet obstruction dogs

Table 1 Weights and histopathological score of bladder and prostate in normal control, BPH control, CMA, Prop, Tam and Prop + Tam treated in the partial outlet obstruction dogs

Drug	Dose (mg/kg)	N	Prostatic weight (g)	Bladder weight (g)	Bladder histopathological score
Normal control	-	4	5.4 ± 1.2	9.3 ± 1.1	2
BPH Control	-	4	17.3 ± 1.5	26.3 ± 9.4	11
CMA	3.2	4	9.9 ± 0.3	15.2 ± 2.5	7
Prop	1	4	18.2 ± 1.6	20.0 ± 6.1	10
Tam	0.1	4	16.3 ± 1.3	24.7 ± 8.6	8
Prop + Tam	1 + 0.1	4	19.6 ± 1.6	14.4 ± 2.3	6

Interpretation of results

It was confirmed that the canine model with steroid-induced BPH with urinary disturbance developed either frequent micturition or the urinary incontinence, providing a useful model for the evaluation of the efficacy and mechanisms of action of drugs for BPH therapy. In the present study, it would seem that CMA also caused selective atrophy of the glandular epithelium, thus resulting in decreased pressure on the urethra and alleviation of urinary disturbance. On the other hand, combination treatment with an anticholinergic agent (Prop) plus an alpha-blocker (Tam) significantly improved urinary disturbance over Prop or Tam alone. It has been reported that alpha-blockers relax the bladder neck and prostate smooth muscle (dynamic component), and anticholinergics reduce detrusor hyperreflexia [1, 3].

Concluding message

The present study suggested combined therapy with anticholinergic agent and alpha-blocker is an effective treatment option in patients with outlet obstruction and overactive bladder.

References

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- [3] Comparison of the effects of various anticholinergic drugs of human isolated urinary bladder. Arch Int Pharmacodyn Ther, 1995, 330:76-89