

EFFECTS OF DA-8010, A NOVEL MUSCARINIC RECEPTOR 3 ANTAGONIST, ON DETRUSOR CONTRACTION OF CYCLOPHOSPHAMIDE INDUCED OVERACTIVE BLADDER RAT MODEL

Hypothesis / aims of study

Antimuscarinic agents have been the mainstay of treatment for overactive bladder (OAB), but anticholinergic side effect like dry mouth remains a shortcoming to limit long-term use [1]. DA-8010 is a novel muscarinic receptor 3 antagonist with greater selectivity for bladder over salivary gland, compared to other antimuscarinic agents [2,3]. Previous studies verified that DA-8010 is highly effective in inhibition of distension-induced rhythmic bladder contraction in normal rats. Hereby, we have investigated the effects of DA-8010 on detrusor contraction in cyclophosphamide (CYP) induced OAB rat model.

Study design, Materials and methods

Ten Sprague-Dawley 8-week-old female rats (200-250g) received intraperitoneal cyclophosphamide (CYP) injection at a dose of 100mg/kg dissolved in distilled water. Three days after CYP injection, cystometrogram was performed under anesthesia. After intraperitoneal injection of Zoletil (Tiletamine+Zolezepam) 0.1cc/100g and Rompun (Xylazine) 0.025-0.04/100g, PE-50 tubing was introduced into the bladder and physiological saline was infused at rate of 0.04ml/min. DA-8010 (0.3mg/kg) or vehicle (control) was administrated via intra-arterial injection after acquisition of baseline data for 40-60 minutes. Intercontraction interval (ICI), basal pressure (BP), threshold pressure (TP), and maximal pressure (MP) were recorded with PowerLab® system. At three consecutive points, ICI, BP, TP and MP were recorded before and after DA-8010 administration respectively, and mean values were compared with paired t-test analysis.

Results ICI of CYP treated OAB rats increased significantly after DA8010 administration (mean 95 ± 35.7 sec) compared to baseline (74.4 ± 25.4 sec) ($P=0.015$). However, other cystometric parameters such as BP, TP, and MP had not changed significantly. All parameters including ICI did not change after vehicle administration.

Interpretation of results

The significant increase of ICI suggest that DA8010 may be an effective agent in treatment of OAB. In addition, the non-significant change of BP, TP, and MP suggest that DA8010 may not debilitate bladder function in micturition.

Concluding message

DA-8010 increased ICI in an OAB rat model without affecting the BP, TP, or MP. These findings suggest that DA-8010 may be effective in the treatment for OAB with minimal side effect of dry mouth.

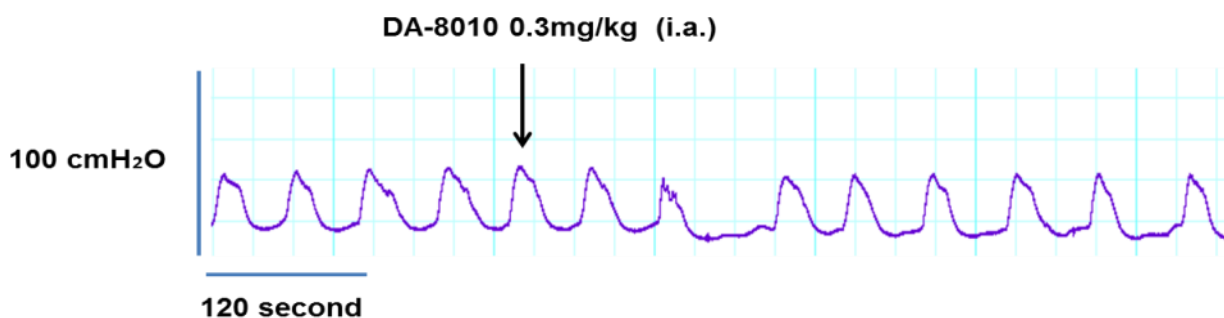
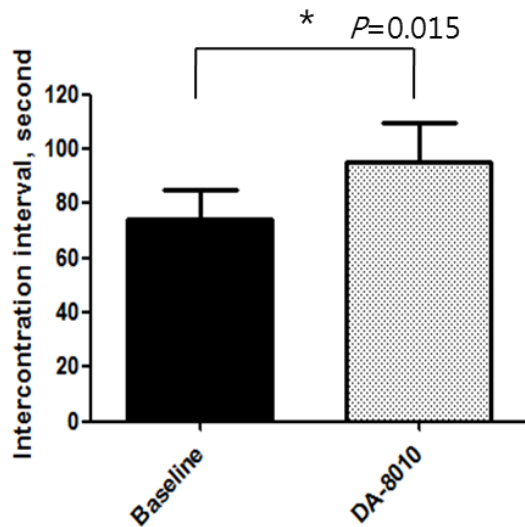
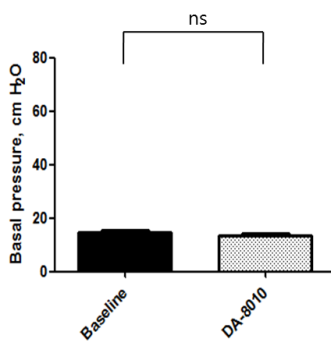


Figure1. Baseline cystometrogram and cystometrogram obtained after DA-8010 intra-arterial administration

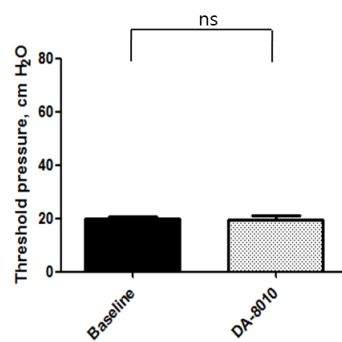
(A)



(B)



(C)



(D)

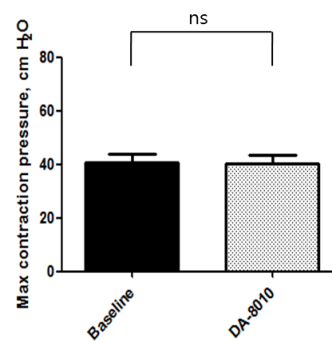


Figure 2. Changes in cystometric parameters after DA-8010 administration

(A) Intercontraction interval, (B) Basal pressure, (C) Threshold pressure, (D) Maximal pressure
*, significant at $P < 0.05$; ns, not statistically significant

References

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Disclosures

Funding: Dong-A ST Research Institute, Yongin-Si, Republic of Korea **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Department of Laboratory Animal Resources, Yonsei Biomedical Research Institute