46

Yamada S[1], Oki T[1], Sakakura K[1], Komoto I[2], Yoshida K[2], Kimura R[1]
1. Department of Biopharmaceutical Sciences, School of Pharmaceutical Sciences, University of Shizuoka, 2. Pharmacokinetics Research Lab., Taiho Pharmaceutical Co.Ltd.

DECLINE OF SALIVARY MUSCARINIC RECEPTOR BLOCKING ACTIVITY OF PROPIVERINE HYDROCHLORIDE BY THE LONG-TERM ADMINISTRATION

Hypothesis / aims of study

Anticholinergic agents such as oxybutynin are widely used for the treatment of overactive bladder (OAB) which is characterized by symptoms of increased frequency of micturition and urge urinary incontinence [1]. However, the major problems with its use are uncomfortable systemic side effects such as dry mouth that can lead to the discontinuation of treatment. Propiverine hydrochloride (Prop) is commonly used for the therapy of OAB [2]. Recently, Noguchi et al. [3] have reported the interesting finding by using visual analog scale, that the feeling of thirst in OAB patients was significantly decreased by 4 weeks consecutive treatment with Prop than the 2 weeks treatment [3]. This clinical observation leads to the idea that the long-term treatment with Prop may cause a significant alteration in the muscarinic acetylcholine receptor (mAChR) binding characteristics of this drug in the salivary gland. To test such assumption, we characterized mAChR binding in the submaxillary gland excised from rats receiving the repeated oral treatment with Prop. Moreover, the pilocarpine-evoked salivary secretion and tissue drug concentration in these rats were simultaneously measured.

Study design, materials and methods

After receiving oral administration of Prop for 2 and 4 weeks, rats were sacrificed by the exsanguination from descending aorta, and the submaxillary gland was excised. mAChR in the tissue homogenate was measured by radioreceptor binding assay with [N-methyl-^{3}H]scopolamine (NMS) as a radioligand, and binding parameters of apparent dissociation constant (Kd) and maximal number of binding sites (Bmax) for [^{3}H]NMS were estimated by Scatchard analysis. The tissue concentration of Prop was measured by the method of LC/MS/MS. Also, the pilocarpine (0.1-10 mg/kg, i.v.)-evoked salivary secretion was measured in rats receiving oral Prop.

Results

A significant increase in Kd for specific [^{3}H]NMS binding in the submaxillary gland of rats without a change in Bmax was observed by the repeated oral administration of Prop (3, 30 mg/kg) for 2 weeks. However, interestingly, similar administration of this drug for 4 weeks caused a significant increase in Bmax for [^{3}H]NMS binding in this tissue with little change in Kd. Also, the inhibitory effect by Prop of pilocarpine-evoked salivary secretion was significantly decreased in rats administered orally this drug for 4 weeks, compared with the inhibition due to a single treatment, and this attenuation by the Prop treatment was more prominent in the salivation of lower dose of pilocarpine. The tissue concentration of Prop was little different between 2 and 4 weeks in the submaxillary gland of rats received repeated oral administration of this drug.

Interpretation of results

These data suggest that repeated oral administration of Prop for 4 weeks compared with 2 weeks causes a significant decline of mAChR binding activities in the submaxillary gland and the concomitant up regulation of the receptor density. Furthermore, the repeated administration of Prop for 4 weeks may reduce significantly the inhibitory effect by this drug of pilocarpine-evoked salivation. It seems unlikely that these effects due to the repeated Prop treatment are ascribed to the altered content of this drug in the submaxillary gland.

Concluding message

The present study has provided the pharmacological evidence to support the idea that the long-term therapy with Prop in OAB patients may be beneficial in terms of reducing the extent of dry mouth.

References

[1] Yarker YE. et al.: Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs & Aging 6: 243-262, 1995.

[2] Madersbacher H, et al.: Efficacy, tolerability and safety profile of Propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). World Urol 19: 324-335, 2001.

[3]Noguchi M, et al.: Differential pharmacokinetics between salivary glands and bladder detrusor muscle with propiverine hydrochloride on over active gladder patients. The International Continence Society 33nd Annual Meeting (Florence), Abstract, pp.323-324, 2003.