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THE ACTIVE METABOLITE (DPR-P-4(N→O)) OF PROPIVERINE HYDROCHLORIDE MAY CONTRIBUTE TO THE BLADDER SELECTIVITY OF THIS DRUG TO TREAT PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study

Anticholinergic agents such as oxybutynin are widely used for the treatment of overactive bladder 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 (propiverine) is commonly used for the therapy of overactive bladder and this drug is generally accepted as a drug exerting relatively less systemic side effects than oxybutynin in patients with overactive bladder [2]. Orally administered propiverine is metabolized in the intestine and liver to form active metabolite, 1-Methyl-4-piperidyl benzilate N-oxide (DPr-P-4(N→O)). Although DPr-P-4(N→O) is assumed to contribute to the muscarinic receptor blockade of parent compound, the pharmacological relevance of this metabolite is not fully understood. To clarify this issue, we have comparatively evaluated *in vitro* muscarinic receptor binding affinity of propiverine and DPr-P-4(N→O) in the bladder and salivary gland of rats and human tissues. Also, we characterized muscarinic receptor binding in the bladder and submaxillary gland excised from rats treated orally with propiverine. In the bladder and submaxillary gland of these rats, the tissue concentrations of propiverine and DPr-P-4(N→O) were simultaneously measured. A part of data is currently presented elsewhere [3].

Study design, materials and methods

After receiving oral administration of propiverine (30 mg/kg), rats were sacrificed by the exsanguination from descending aorta, and the bladder and submaxillary gland were excised. The muscarinic receptors in rat and human tissue (bladder and salivary gland) homogenates was measured by radioreceptor binding assay with [N-methyl-^{3}H]scopolamine ([^{3}H]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 concentrations of propiverine and DPr-P-4(N→O) were measured by the method of LC/MS/MS.

Results

The specific [^{3}H]NMS binding in the bladder and submaxillary gland of rats was inhibited by propiverine and DPr-P-4(N→O) in a concentration-dependent manner. The inhibitory effect of propiverine and DPr-P-4(N→O) in the submaxillary gland was slightly greater than in the bladder. At 1, 3, 6 and 12 h after oral administration of propiverine, there was significant and consistent increase of Kd for specific [^{3}H]NMS binding in the rat bladder, while the propiverine administration showed only transient muscarinic receptor binding in the submaxillary gland at 1 and 3 h. These data suggest significant and long-lasting occupancy of muscarinic receptors by oral propiverine in the bladder than in the salivary gland. Interestingly, the measurement of tissue concentration revealed markedly higher concentration of DPr-P-4(N→O) in the bladder than in the submaxillary gland of rats received oral propiverine, while there was similar concentration of propiverine in these tissues. Further, it has been shown that propiverine and DPr-P-4(N→O) inhibited concentration-dependently specific [^{3}H]NMS binding in homogenates of human bladder and parotid gland. Based on ratios of Ki values, the inhibitory effect of DPr-P-4(N→O) was 1.6 times greater in the bladder than in the parotid gland, whereas the inhibitory effect of propiverine was 2 times greater in the parotid gland.

Interpretation of results

These data suggest that DPr-P-4(N→O) formed in the blood of rats after oral administration of propiverine distributes at the higher concentration in the bladder than in the salivary gland, and this metabolite binds continuously to muscarinic receptors in the bladder. If such high accumulation of DPr-P-4(N→O) would last also in the bladder of patients with overactive bladder after oral treatment with propiverine as observed in rats, it is considered that this metabolite causes high bladder selectivity, due to the higher affinity of muscarinic receptors in the human bladder than in the salivary gland [3].

Concluding message

The present study has provided the first pharmacological evidence to support the idea that the active metabolite, DPr-P-4(N→O) may contribute largely to the bladder selectivity in patients with overactive bladder who were treated with propiverine.

References:

[1] Drugs & Aging 6: 243-262, 1995.

[2] World Urol 19: 324-335, 2001.
[3] J Urol 175: 365-369, 2006.

FUNDING: NONE
DISCLOSURES: NONE
ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Shizuoka, University of Yamanashi