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HIGH CONCENTRATION OF DRUG DISTRIBUTION MAY CONTRIBUTE TO THE BLADDER-SELECTIVE PHARMACOLOGICAL EFFECT OF IMIDAFENACIN, A NOVEL ANTIMUSCARINIC AGENT, FOR THE TREATMENT OF OVERACTIVE BLADDER

Hypothesis / aims of study

A novel antimuscarinic agent, imidafenacin is currently developed for the therapy of overactive bladder (OAB) in Japan. It was reported that imidafenacin exhibited functional selectivity for the bladder over the salivary gland and also high doses of this drug had little pharmacological effect on the central nervous system (CNS). With regard to the pharmacokinetics, the serum concentration of imidafenacin peaked at 0.2 h after oral administration of this drug in rats, and it declined rapidly. The present study was undertaken to examine the bladder selectivity on the basis of in vivo muscarinic receptor (mAChR) binding of oral administration of imidafenacin in relation to the pharmacokinetics in rats. Furthermore, the possibility that imidafenacin excreted into urine may be partly to the therapeutic effect was examined by the intravescial injection of this drug.

Study design, materials and methods

At 1 to 12 h after oral administration of imidafenacin (1.57, 6.26 μmol/kg), rats were sacrificed by the exsanguination from descending aorta, and the bladder, heart, colon, lung and brain were excised. mAChRs in tissue homogenates were measured by the radioligand binding assay using [N-methyl-^{3}H]scopolamine (NMS), a selective radioligand of mAChR, and binding parameters of apparent dissociation constant (Kd) and maximal number of binding sites (Bmax) for [^{3}H]NMS were estimated by nonlinear regression analysis using Graph Pad Prism. In addition, rats received intravesical infusion of imidafenacin for the bladder mAChR measurement. The serum and tissue concentrations of imidafenacin in rats for the analysis of pharmacokinetics were measured by the method of LC/MS.

Results

The in vitro binding assay by using [^{3}H]NMS demonstrated the mAChR binding of imidafenacin with extremely higher affinity than other antimuscarinic agents. In the bladder of rats after oral administration of imidafenacin at the pharmacologically relevant dose (1.57, 6.25 □mol/kg), there was a significant and sustained binding of mAChR lasting until at least 9 h, as revealed by the increase of [^{3}H]NMS (Table 1). On the other hand, in these rats, the mAChR binding was transient in other organs such as the submaxillary gland and was little observed in the brain. These data may underlie the greater selectivity of imidafenacin in pharmacological effects in the bladder than in the salivary gland and brain. As shown in Fig. 1, the pharmacokinetic study has revealed that much higher concentration of imidafenacin was distributed in the bladder than in the submaxillary gland of rats received oral doses (1.57 and 6.26 mol/kg) of this drug. The intravesical injection of imidafenacin at similar concentrations of this drug as excreted in human urine showed significant binding of mAChR in the bladder of rats but not in other tissues.

Interpretation of results

Oral administration of imidafenacin exerted a longer-lasting binding of mAChR in the bladder of rats than other organs such as the submaxillary gland. The higher concentration of imidafenacin was detected in the bladder than in the salivary gland, suggesting selective binding of mAChR in the target organ to treat overactive bladder. The excreted imidafenacin in the urine may bind directly to the bladder mAChR. It is speculated that similar mechanism as observed in the present underlies the pharmacological specificity (relatively less incidence of dry mouth) of imidafenacin in patients with overactive bladder. The present study has provided the first in vivo convincing evidence substantiating the bladder selectivity of imidafenacin.

Concluding message

Imidafenacin exerts a selective and sustained binding of mAChR in the bladder, possibly due to the pharmacokinetic profile of greater tissue distribution.

Table 1 Kd and Bmax for specific [^{3}H]NMS binding in the bladder, submaxillary gland, and brain of rats at 1 to 12 hr after oral administration of imidafenacin (6.26 μmol/kg).

Tissues	Time (hr)	Kd (pM)	Bmax (fmol/mg protein)
Bladder	Control	275 ± 6	146 ± 8
	1	362 ± 13 (1.32)**	131 ± 7
	3	346 ± 30 (1.26)**	140 ± 9
	6	336 ± 21 (1.22)*	126 ± 5
	9	338 ± 13 (1.23)*	143 ± 10
	12	285 ± 23	178 ± 1
Submaxillary gland	Control	185 ± 6	116 ± 5
	1	294 ± 19 (1.59)**	110 ± 7
	3	364 ± 39 (1.97)**	114 ± 8
	6	228 ± 5	97 ± 5
	9	195 ± 12	122 ± 6
	12	222 ± 9	111 ± 9
Brain	Control	231 ± 5	1107 ± 31
	1	257 ± 34	980 ± 17
	3	252 ± 19	1034 ± 48
	6	234 ± 5	975 ± 59

9	254 ± 11	1099 ± 20
12	236 ± 7	1054 ± 69

Values are mean ± S.E. of 16 (control) and 4 to 6 (imidafenacin) rats. Values in parentheses represent the fold-increase in Kd values relative to control. Asterisks show a significant difference from the control values, *P<0.05, **P<0.01.

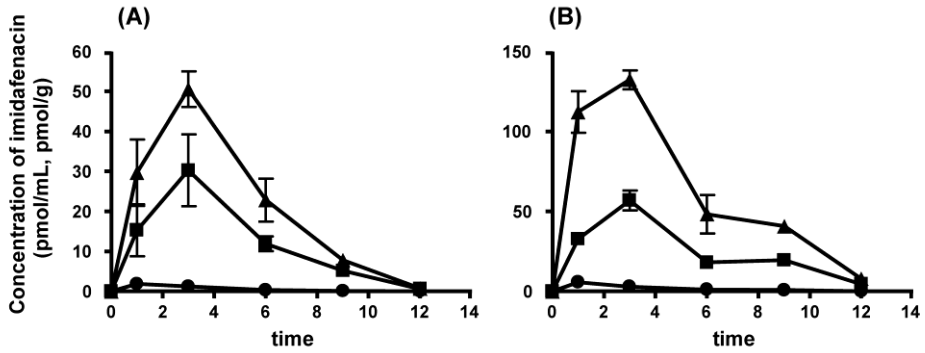

Fig. 1. Time course of concentrations of imidafenacin in serum (●), bladder (▲) and submaxillary gland (■) of rat after oral administration of imidafenacin. Rats received imidafenacin (1.57 (A) and 6.26 (B) μmol/kg) orally, and serum, bladder and submaxillary gland samples were collected until 12 hr. Each point represents mean ± S.E. of 3 (serum), 3 (bladder) and 2 to 3 (submaxillary gland) rats.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**This study was done in accordance with recommendations of the US National Institutes of Health and the Experimental Animal Ethical Committe of the University of Shizuoka.**