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PHARMACOKINETICS OF IMIDAFENACIN, A NOVEL ANTIMUSCARINIC AGENT, MAY CONTRIBUTE LARGELY TO THE BLADDER-SELECTIVE PHARMACOLOGICAL EFFECTS

Hypothesis / aims of study

Imidafenacin, a novel antimuscarinic agent, 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 even high doses of this drug had little pharmacological effect on the central nervous system (CNS) [1-3]. The present study was aimed to clarify the underlying mechanism for bladder selectivity on the basis of in vivo muscarinic receptor (mAChR) binding of oral administration of imidafenacin in rats in relation to the pharmacokinetics. We characterized muscarinic receptor binding in various tissues and pharmacokinetics in rats after oral and intravesical administration of imidafenacin.

Study design, materials and methods

Following oral and intravesical administration of imidafenacin at various doses, muscarinic receptors in six tissues (bladder, submaxillary gland, heart, colon, lung, brain) of rats were simultaneously measured by radioligand binding assay using [*N*-methyl-^{3}H] scopolamine methyl chloride ([^{3}H]NMS), a selective radioligand of mAChR. 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. Pharmacokinetic parameters were estimated from measurements of the concentration of imidafenacin in serum, the bladder, the submaxillary gland and urine by the method of LC/MS/MS.

Results

In vitro binding assay by using [^{3}H]NMS demonstrated 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 (0.79, 1.57, 6.25 μmol/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. 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 results may underlie the greater selectivity of imidafenacin in pharmacological effects in the bladder than in the salivary gland and brain. The intravesical injection of imidafenacin at similar concentrations (30-3000 nM/0.2 mL/rat, 30 min) of this drug as excreted in human urine showed significant binding of mAChR in the bladder of rats but not in other tissues (Table 1). Moreover, pharmacokinetic data showed that orally administered imidafenacin distributed at a higher concentration in the bladder than the serum or submaxillary gland of rats (Fig. 1). Furthermore, a significant level of imidafenacin (231 nM) was detected in the urine of rats given these pharmacological dose (1.57 μmol/kg) of this agent.

Interpretation of results

These results showed that imidafenacin administered orally distributes predominantly to the bladder and exerts more selective and longer-lasting effect on the bladder than other tissues such as the submaxillary gland, colon and brain. Furthermore, the imidafenacin excreted in urine may play an important role in the pharmacokinetic and pharmacological selectivity.
It is speculated that similar mechanism as observed in the present study underlies the pharmacological specificity (relatively less incidence of dry mouth) of imidafenacin in patients with overactive bladder.

Concluding message

Imidafenacin exerts a selective and sustained binding of mAChR in the bladder, possibly due to the pharmacokinetic profile of greater tissue distribution. The present study has provided the first in vivo convincing evidence substantiating the bladder selectivity of imidafenacin.

Table 1. K_d and B_{max} for specific [^{3}H]NMS binding in the bladder, submaxillary gland, and heart of rats after the intravesical instillation of imidafenacin. Rats received 30 - 3000 nM/0.2 mL/rat of imidafenacin intravesically, and were sacrificed 0.5 h later. Specific binding of [^{3}H]NMS (0.06-1.5 nM) in rat tissues was measured. Values in parentheses represent the fold-increase in K_d values relative to the control.

Tissues	Imidafenacin	K_d (pM)	B_{max} (fmol/mg protein)
Bladder	Control	247 ± 14 (1)	135 ± 15
	30 nM	338 ± 20 (1.37)*	155 ± 11
	300 nM	354 ± 24 (1.43)*	161 ± 19
	3,000 nM	399 ± 49 (1.62)**	157 ± 15
Submaxillary gland	Control	182 ± 11	130 ± 12
	30 nM	168 ± 8	118 ± 5
	300 nM	200 ± 8	123 ± 9
	3,000 nM	176 ± 13	137 ± 11
Heart	Control	359 ± 21	83.8 ± 3.8
	30 nM	330 ± 59	75.4 ± 11.9
	300 nM	353 ± 16	84.4 ± 2.7
	3,000 nM	403 ± 23	84.1 ± 3.1

Values are the mean ± S.E. for five (control) and four to five (imidafenacin) rats.
Asterisks show a significant difference from the control values, *P<0.05, **P<0.01.

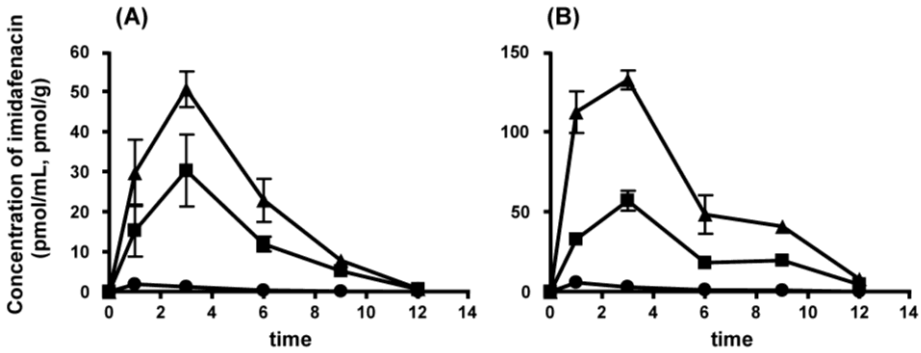

Fig. 1. Time course of concentrations of imidafenacin in serum (●), bladder (▲) and submaxillary gland (■) of rat after oral administration of imidafenacin. Rats received imidafenacin (1.57 (A) and 6.26 (B) μmol/kg) orally, and serum, bladder and submaxillary gland samples were collected until 12 hr.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

References
1. Arzneimittel-Forschung, 57: 147-154 (2007)
2. Int J Urol, 16: 499-506 (2009)
3. J Pharmacol Exp Ther, 336: 365-371 (2011)

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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