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IN VIVO BLADDER SELECTIVITY PROFILE OF IMIDAFENACIN, A NOVEL ANTIMUSCARINIC AGENT, ASSESSED BY BLADDER CAPACITY-INCREASING ACTIVITY AS AN EFFECTIVENESS INDEX IN RATS

Hypothesis / aims of study

Several antimuscarinic agents with high-bladder selectivity have been developed and commonly used for treating overactive bladder (OAB). The problem of antimuscarinics, however, is anticholinergic-based side effects, such as dry mouth, constipation, and tachycardia, and still remains to be fully solved. Recent studies have revealed that antimuscarinic agents exert their therapeutic action by increasing bladder capacity based on acting through the bladder sensory nerves and/or bladder urothelium rather than the detrusor muscle. In fact, the bladder capacity increase is clinically observed at dose levels less than those at which antimuscarinics decreased micturition pressure [1]. In animal studies, however, the effect on the detrusor muscle, mainly the inhibition of intravesical pressure, has been used as an effectiveness index in assessing the bladder selectivity of antimuscarinisc agents [2]. Imidafenacin, 4-(2-Methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide, is a novel antimuscarinic agent for OAB-treatment approved in Japan in 2007. We, therefore, reevaluated the bladder selectivity of imidafenacin and other antimuscarinics (solifenacin, tolterodine, and propiverine) by comparing the bladder capacity-increasing effect with anticholinergic effects on salivary gland, colon, and heart among them.

Study design, materials and methods

The present study used urethane-anesthetized Spradue Dawley rats in all experiments. Bladder capacity was intermittent-cystometrically measured as the amount of saline infused into the bladder at the time when micturition occurred. We removed the residual urine from the bladder after each micturition. Anticholinergic side effects were monitored as the inhibitory actions each on salivation induced by electrical stimulation of chorda tympani, on rhythmical contraction induced by raising the internal pressure in colon, and on carbamylcholine-induced bradycardia. All drugs were intravenously administered 15 min before measurements. The dose ratio was calculated by dividing the 50% inhibitory dose (ID50) for each anticholinergic side effect by the maximum effective dose to increase bladder capacity. The bladder selectivity was expressed as relative ratios to the dose ratio of propiverine.

Results

Imidafenacin, solifenacin, tolterodine, and propiverine increased bladder capacity in a dose-dependent manner and exerted the maximum effect at 0.003, 1, 0.03, 3 mg/kg, respectively. Furthermore, the three drugs, except for propiverine, did not affect either of the micturition pressure and the residual volume at the maximum effective dose. When a bladder capacity-increasing effect was used as an effectiveness index, each bladder selectivity of imidafenacin, solifenacin, and tolterodine was: 15, 1.7, 2.5-fold higher over salivary gland; 150, 1.9, 9.2-fold higher over colon; and 50, 12, 4.6-fold higher over heart, respectively, than that of propiverine (Table). As an additional experiment on heart rate, we examined the influence of imidafenacin on baroreflex in conscious rats, but found no influence of imidafenacin at least by 0.3 mg/kg which corresponded to the 100 times the maximum effective dose.

Interpretation of results

When a bladder capacity-increasing effect was used as an effectiveness index in assessing bladder selectivity, imidafenacin was most highly selective for urinary bladder over salivary gland, colon and heart among antimuscarinic agents used. The results of bladder selectivity in this study are somewhat different from those in the previous studies using the inhibition of detrusor contractility as an effectiveness index [2]. This discrepancy appears to be based on difference in effectiveness indices (bladder capacity and intravesical pressure), because the potency rank order in anticholinergic side effects among the drugs is almost similar to the previous results [2].

Concluding message

These results may provide a therapeutic benefit of imidafenacin in OAB-treatment with less major anticholinergic side effects such as dry mouth, constipation and tachycardia than other antimuscarinic agents used.

Table

The bladder selectivity of each antimuscarinic agent over salivary gland, colon, and heart in urethane-anesthetized rats

Drug	Bladder	Salivary gland		Colon		Heart	
	MED a) (mg/kg)	ID50 (mg/kg)	Selectivity b)	ID50 (mg/kg)	Selectivity b)	ID50 (mg/kg)	Selectivity b)
Imidafenacin	0.003	0.0078	15	1.8	150	0.0090	50
Solifenacin	1	0.30	1.7	7.4	1.9	0.71	12
Tolterodine	0.03	0.013	2.5	1.1	9.2	0.0082	4.6
Propiverine	3	0.52	1	12	1	0.18	1

a) MED: Maximum effective dose.

b) The dose ratio was calculated by dividing the ID50 value by the MED, and then the selectivity was expressed as relative ratios to the dose ratio of propiverine.

MEDs and ID50 values represent means of five experiments.

References

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Specify source of funding or grant	**Kyorin Pharmaceutical Co., Ltd. funded this study because all the authers are employed by the campany.**
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	**The protocols and animal care complied with the Guiding Principles for the Care and Use of Laboratory Animals recommended by The Japanese Pharmacological Society, and according to the standard operating procedures for institutional animal care management in our facility**