Comparative Influence of Imidafenacin and Oxybutynin on Voiding Function in Rats with Functional Urethral Obstruction

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Key words
- overactive bladder
- benign prostatic hyperplasia
- imidafenacin
- oxybutynin
- urinary flow

Abstract

An antimuscarinic therapy may increase the risk of voiding dysfunction. However, it is unclear whether the relative risk of voiding dysfunction is different among antimuscarinics. Therefore we determined the potencies both in enhancing the bladder capacity (BC), effectiveness, and in decreasing the maximum urinary flow rate (Qmax), voiding dysfunction, to compare their therapeutic indices.

Under urethane anesthesia, urinary flow rate was measured at distal urethra using an ultrasonic flow meter in female Sprague-Dawley rats with functional urethral obstruction induced by a continuous i.v. infusion of α_1-adrenoceptor agonist A-61603 (0.03 µg/kg/min). In a separate group of urethane-anesthetized rats without urethral obstruction, an intermittent cystometry was performed to determine BC.

Intravenous imidafenacin and oxybutynin produced a significant dose-dependent decrease in Qmax with the minimum doses of 0.03 and 1 mg/kg, respectively. Imidafenacin and oxybutynin markedly increased BC, with minimum doses of 0.01 and 3 mg/kg, respectively. At the minimum dose to increase BC, oxybutynin caused a significant increase in residual urine volume with a significant decrease in voiding efficiency, whereas imidafenacin had no influence on these values. The relative influence index, which is the ratio of the minimum influence dose between in decreasing of Qmax and in increasing of BC, of imidafenacin was 10 fold higher than that of oxybutynin.

This study suggests that imidafenacin has a lower relative risk of voiding difficulty compared with oxybutynin in rats. These results provide new information that antimuscarinics may have varying degrees of impact on voiding difficulty.

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Introduction

Antimuscarinic drugs are widely used for treatment of overactive bladder (OAB), which is characterized by storage symptoms, such as urinary urgency. Although the clinical efficacy of antimuscarinics has been well established, their mechanism-based adverse reactions often result in poor compliance and in turn limiting their clinical usefulness. The most common and bothersome of such adverse reactions include dry mouth and constipation [1]. Another significant concern and potentially harmful reaction of antimuscarinics is acute urinary retention (AUR) in male patients, especially those with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), and indeed OAB symptoms frequently accompany BPH [2–4]. Because muscarinic receptors (mainly via M_3 subtype) play a pivotal role in contracting detrusor smooth muscles, antimuscarinics theoretically have an ability to induce AUR [5]. In addition, BPH per se is typically responsible for AUR because of intrinsically narrowed urethra. Thus, prescribing antimuscarinics for BPH patients could further aggravate voiding dysfunction. Nevertheless, some data from recent clinical trials suggest that the incidence of AUR in antimuscarinic therapy is infrequent (< 1 %), even in male patients with BPH [1]. However, the results reported may have underestimated the true incidence of this adverse reaction, because these trials were of short duration and included the patients with low post-void residual urine volume (RV) at baseline. Indeed, Radomski [6] described, according to his database study that AUR risk is somewhat higher (the rate of 2.5 %) in real life clinical practice. Furthermore, above-mentioned clinical trials have consistently been reported to increase the post-void RV in antimuscarinic therapy, indicating the

impairment of voiding function [1]. Therefore, despite the absence of definitive evidence, it is recommended that OAB patients, especially those associated with BPH, should be carefully monitored for post-void RV to avoid inadvertent AUR during the antimuscarinic therapy [7].

Adverse reaction profiles of the existing antimuscarinics may be different depending on their selectivity for specific subtypes of muscarinic receptor, their tissue selectivity (organ specificity) for bladder, their physicochemical properties, as well as their pharmacokinetic properties [1]. In fact, clinical studies have shown that a new generation of antimuscarinics with higher selectivity for the M_3 muscarinic receptor subtype and/or bladder tissue has a comparable efficacy with first-generation antimuscarinic oxybutynin but has fewer adverse reactions, mainly dry mouth [8]. On the other hand, diminishing adverse effects on voiding function was probably considered more difficult to achieve, because antimuscarinics had been traditionally believed to exert their therapeutic action on OAB by reducing detrusor muscle contraction via blockade of M_3 subtype [9]. More recently, however, Finney et al. [10] found that at least in a range of usual therapeutic doses, antimuscarinics primarily act during storage phase of micturition cycle, resulting in decreasing urgency and increasing bladder capacity (BC), whereas they have little or no influence on detrusor muscle contraction during voiding phase. Similarly basic researches with experimental animal models of OAB have reported that low doses of antimuscarinics significantly increase BC without influence on voiding contractions, and their increasing effect is significantly inhibited by sensory denervation induced by resiniferatoxin [11]. These findings suggest that some regulatory involvement of antimuscarinics in afferent nerve activity during the storage phase contributes to their therapeutic effect, but such involvement may be absent in efferent activity during voiding phase.

Imidafenacin, 4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide, belongs to a new generation of antimuscarinics with high affinity for the M_1/M_3 muscarinic receptor subtypes and high bladder selectivity [12,13], and was approved for treating OAB in Japan in 2007. A randomized, double-blind, controlled trial (RCT) demonstrated that imidafenacin is as efficacious as a first-generation antimuscarinic drug propiverine but has better adverse reaction profiles [14]. Antimuscarinics are currently recommended as a useful addition to drug regimens for BPH patients with predominantly OAB symptom. Recent RCTs in male BPH patients with OAB symptoms reported that antimuscarinics, including propiverine, tolterodine, and solifenacin, in combination with α_1-adrenoceptor antagonist, caused AUR, though the incidence was considerably low (<2% in all of these trials) [15–17]. In a similar RCT no patients experienced AUR when imidafenacin was combined with α_1-adrenoceptor antagonist tamsulosin [18]. And the post-void RV in this combination treatment was statistically different from that in tamsulosin treatment alone [18]. These clinical findings led us to hypothesize that imidafenacin may have a different degree of inducing risk of voiding dysfunction from other existing antimuscarinics. It is practically difficult, however, to directly compare the clinical data of different antimuscarinics each other, because of differences in various conditions, such as the treatment protocol/design and the baseline severity of BPH. Therefore, to prove our hypothesis, we evaluated the effectiveness (increasing the BC) and the voiding dysfunction (decreasing the maximum urinary flow rate (Qmax)) in rats when treated with imidafenacin and oxybutynin each alone, and compared their relative risk of voiding dysfunction in terms of relative therapeutic index. Oxybutynin was selected for comparison because it was a representative of the first-generation of antimuscarinic drugs that has been intensively investigated for the AUR [19].

Materials and Methods

Animals

Female Sprague-Dawley rats (Charles River Laboratories Japan, Kanagawa, Japan), weighing 210–280 g, were housed in a room maintained under controlled conditions 23±3 °C, 55±15% RH, and 12:12-h light-dark cycle. The rats had free access to food pellets and tap water. All animal care/experiments and the study protocol complied with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals and were approved, prior to the study, by the Institutional Animal Ethics Committee at Kyorin Pharmaceutical Co., Ltd. Our facility is certified as an animal testing research institute by the Japan Health Sciences Foundation, established under the jurisdiction of the Japanese Ministry of Health, Labor and Welfare.

Pressure-flow measurement in urethane-anesthetized rats with functional urethral obstruction

Pressure-flow study (a simultaneous recording of urinary flow rate and intravesical pressure) was performed by a slight modification of the method reported by Streng et al. [20]. Although Streng et al. used the continuous cystometry in their study, we used the intermittent cystometry, because the continuous cystometry does not allow to measure the residual urine volume. In brief, under urethane anesthesia (1.2 g/kg, s.c.), a lower abdominal midline incision was made to expose the bladder. A saline-filled polyethylene catheter (PE50; Japan Becton Dickinson, Tokyo, Japan) was inserted into the bladder dome. The catheter was connected via a 3-way cock to a pressure transducer (Nihon Kohden, Tokyo, Japan) for measurement of the intravesical pressure and to a syringe pumps (Harvard Apparatus, Holliston, MA, USA) for saline infusion. The bone of symphysis pubis was cut vertically to expose the urethra. An ultrasonic flow probe (MC2.5PSB; Transonic Systems, Ithaca, NY, USA) was placed around the distal urethra and connected to a transit-time flow meter (TS420, Transonic Systems) for the measurement of actual urinary flow rate. The intravesical pressure and the urinary flow rate were recorded at a sampling rate of 400 Hz using PowerLab system (AD Instruments Pty Ltd, Castle Hill, Australia). The influence of antimuscarinics on the urinary flow rate was assessed under a partial urethral obstruction induced by a selective α_1-adrenoceptor agonist A-61603 (i.e., functional urethral obstruction), because in the preliminary examination, treatment with each antimuscarinic drug alone even if at higher doses resulted in too much residue of Qmax (approximately 50% to Qmax in normal rats) to evaluate the effects of antimuscarinics on voiding function. The functional urethral obstruction was induced according to a modification of the method of Nagabukuro et al. [21]. In the present study, A-61603, a potent selective α_{1A}-adrenoceptor agonist [22], instead of phenylephrine, was used in order to induce the urethral obstruction, because A-61603 affected less on blood pressure than phenylephrine at the dose causing the similar-level of Qmax decrease by phenylephrine in urethane anesthetized rat in our preliminary experiments. In brief, at least 30-min after surgery, saline was infused into the bladder at a rate of 0.06 mL/min in order to confirm the recovery

of micturition reflexes (priming). And then, A-61603 (0.03 µg/kg/min) was continuously infused into the jugular vein at a rate of 0.01 mL/min. After several micturitions occurred, the saline infusion was stopped and residual urine was removed from the bladder. 10 min later, saline was reinfused into the bladder until micturition was evoked and then the residual urine was removed again. The procedures were repeated at 10-min intervals until 2 similar consecutive responses (cystometrogram and flowmetrogram patterns) were obtained (pre-treatment value). 5 min after the last micturition, each antimuscarinic drug was intravenously administered to the rat via the femoral vein. 5 min after drug treatment, the same procedure as described in the measurement of pre-treatment value was repeated twice. Changes in the second patterns each of cystometrogram and flowmetrogram during this period was used for analysis of post-treatment value.

Bladder capacity measurement in urethane-anesthetized rats

Effects of antimuscarinics on BC were evaluated using a separate group of urethane-anesthetized rats without partial urethral obstruction, because the preliminary examination confirmed that A-61603 per se induced a 2.4-fold extension of intercontraction intervals in urethane anesthesia rats, and because of this extension, BC-increasing effects of the antimuscarinics failed to detect. The BC was measured by the method Yamazaki et al. reported [13]. In brief, under urethane anesthesia (1.2 g/kg, s.c.), a lower abdominal midline incision was made to expose the bladder. A saline-filled polyethylene catheter (PE50) was inserted into the bladder dome. The catheter was connected via a 3-way cock to a pressure transducer for measurement of the intravesical pressure and to a syringe pumps for saline infusion. The intravesical pressure was recorded at a sampling rate of 400 Hz using PowerLab system. At least 30-min after surgery, saline was infused into the bladder at a rate of 0.06 mL/min in order to confirm the recovery of micturition reflexes (priming). After several micturitions occurred, the saline infusion was stopped and the residual urine was removed from the bladder. 10 min later, saline was reinfused into the bladder until micturition was evoked and then the residual urine was removed again. The procedures were repeated at 10-min intervals until 2 similar consecutive responses were obtained (pre-treatment value). 5 min after the last micturition, each antimuscarinic drug was intravenously administered to an individual rat via the femoral vein. 5 min after drug treatment, the same procedure as described in the measurement of pre-treatment value was repeated twice. Change in the second pattern of cystometrogram was used for analysis of post-treatment value. The post-void RV was measured by gravimetric method.

Drugs

Imidafenacin was synthesized by Kyorin Pharmaceutical Co., Ltd (Tokyo, Japan). Oxybutynin chloride and A-61603 hydrate were purchased from Sigma-Aldrich Japan (Tokyo, Japan). Imidafenacin was dissolved in saline with 1 mol/L hydrochloric acid, then neutralized with 1 mol/L sodium hydroxide, and serially diluted with saline to desired concentrations. Oxybutynin chloride and A-61603 hydrate were dissolved in saline and diluted with saline to desired concentrations, when necessary. The dose levels of the drugs used in this study were set up based on the results of preliminary studies.

Data analysis

All data are expressed as mean ± S.E.M. In the pressure-flow study, the numerical variables relating to the voiding, Qmax, maximum intravesical pressure (Pves max), and intravesical pressure at Qmax (Pves Qmax) were derived from data obtained in pressure-flow measurement. The influences of antimuscarinics on these parameters are expressed as a ratio of post- to pre-treatment value. In BC measurement, BC, the variable relating to bladder function during the storage phase, and maximum intravesical pressure (IVPmax), the variable relating to the voiding, were derived from data obtained by cystometry. The voiding efficiency (VE) was calculated from a formula of (BC-RV)/BC × 100. The influences of antimuscarinics on these parameters are expressed as a ratio of post- to pre-treatment value. Influence index was calculated as the ratio of minimum effective dose in Qmax to that in BC. Statistical analysis was performed by paired, 2-tailed Student's t-test for comparison between 2 groups or by one-way ANOVA followed by Dunnett's post-hoc test for multiple group comparison. In all comparisons, $P < 0.05$ was considered statistically significant.

Results

Pressure-flow measurement in rats with partial urethral obstruction

To evaluate the inhibitory effects of antimuscarinics on the urinary flow rate, the dose of A-61603 (0.03 µg/kg/min, i. v. infusion) that induces a modest level of functional urethral obstruction was determined on the basis of the preliminary data of dose-response relationship. This dose of A-61603 caused a significant partial reduction of Qmax to approximately 24% ($P < 0.001$), accompanied with a significant increase in Pves max and Pves Qmax to approximately 21 and 9%, respectively (**Fig. 1a, b**).

In rats with the partial urethral obstruction, imidafenacin and oxybutynin significantly decreased Qmax in a dose-dependent manner, with minimum influence doses of 0.03 ($P < 0.01$ vs. pre-treatment value, approx. 37% inhibition) and 1 mg/kg ($P < 0.01$ vs. pre-treatment value, approx. 38% inhibition), respectively (**Fig. 2a**). The maximum inhibition of Qmax induced by imidafenacin and oxybutynin were 49% and 38%, and these values were not significantly different each other. In addition to these, imidafenacin and oxybutynin dose-dependently decreased Pves max (up to 31% and 33% inhibition, respectively) and Pves Qmax (up to 15% and 15% inhibition, respectively), both in almost the same dose range as in decreasing the Qmax (**Fig. 2b,c**). These results suggest that both of the antimuscarinics reduce Qmax by inhibiting detrusor contractions during voiding phase. Under the same experimental conditions, vehicle treatment showed no influence on these values.

Bladder capacity measurement in rats

Imidafenacin and oxybutynin significantly caused a dose-dependent increase in BC, with minimum influence doses of 0.01 ($P < 0.01$ vs. vehicle group, 57% increase) and 3 ($P < 0.01$ vs. vehicle group, 53% increase) mg/kg, respectively (**Fig. 3a**). The maximum increases of BC by imidafenacin and oxybutynin were 57% and 56%, these values were not significantly different. Under the same experimental conditions, vehicle treatment showed no influence on these values. Furthermore, both imidafenacin and oxybutynin dose-dependently influenced void-

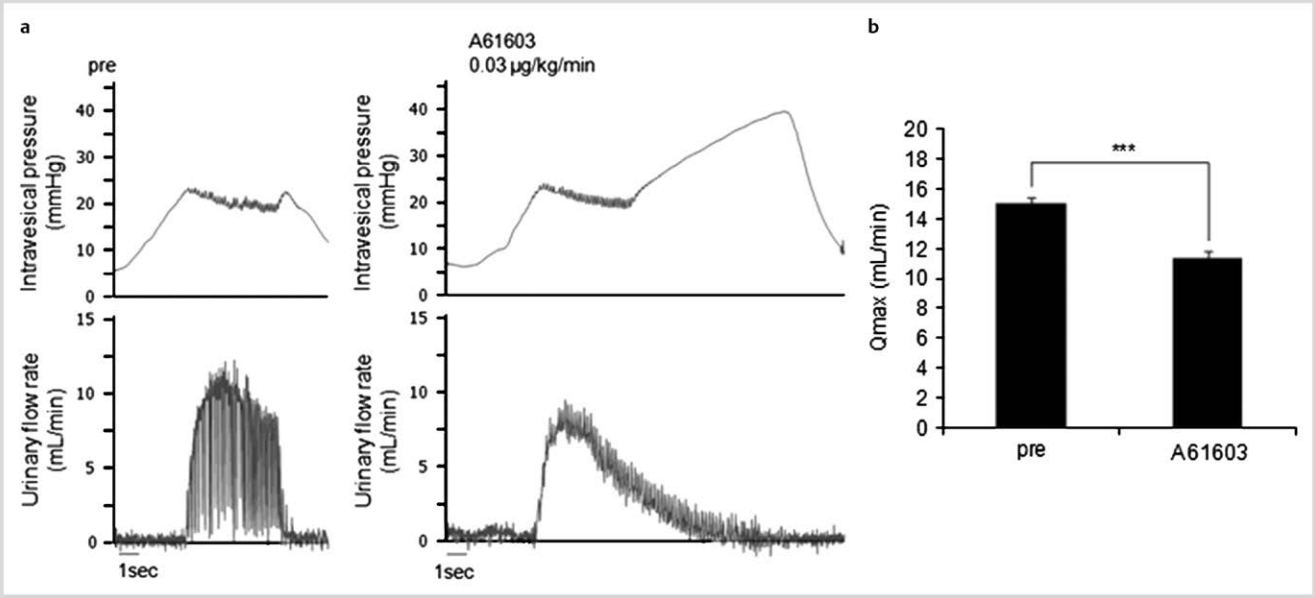

Fig. 1 A typical trace of intravesical pressure and urinary flow rate **a**, and changes in Qmax **b** between pre- and post-injection of A-61603 in urethane-anesthetized rats. A-61603 was infused continuously (0.03 µg/kg/min) into jugular vein. Each column and bar presents the mean ± standard error of the mean of 45 animals. *** $P<0.001$ vs. pre value (student's paired *t*-test). *A61603;* A-61603 hydrate.

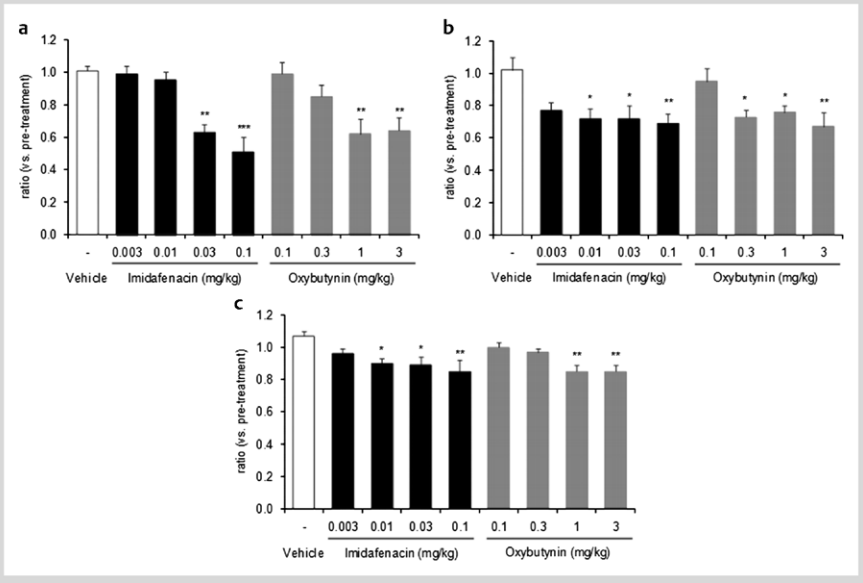

Fig. 2 Effects of imidafenacin and oxybutynin on maximum flow rate **a**, maximum intravesical pressure **b**, and intravesical pressure at Qmax **c** in rats with functional urethral obstruction. Vehicle, imidafenacin, and oxybutynin were administered intravenously. Data are expressed as a ratio of post- to pre-treatment value. Each column and bar represents the mean ± standard error of the mean of 5 animals. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs. vehicle group (Dunnett's multiple comparison test). *Oxybutynin;* oxybutynin chloride.

ing-related variables such as RV and VE. Specifically, at the minimum influence dose to increase BC, oxybutynin tended to influence on IVPmax ($P=0.08$, decrease in 25%) and resulted in significant influence on RV ($P<0.01$, increase in 411%) and VE ($P<0.001$, decrease in 51%), whereas imidafenacin had no influence on these parameters (**Fig. 3b,c,d**). Under the same experimental conditions, vehicle treatment showed no influence on these values.

The resultant relative influence index (i.e., minimum effective dose ratio of Qmax/BC) of imidafenacin was 3 vs. 0.3 for oxybutynin, and thus10 fold higher than that of oxybutynin.

Discussion

The present study revealed that imidafenacin has less influence on voiding function than oxybutynin in rats. These results provide new information that antimuscarinics may have varying degrees of impact on voiding function.

Indeed, many studies have evaluated the functional bladder selectivity of antimuscarinics in various animals, mainly by focusing on dry mouth and constipation. In relation to AUR, some studies have compared and reported the influences of antimuscarinics on the IVP max (or RV) and on the effectiveness such as the BC increasing effect. Yamazaki et al. [13] reported that imidafenacin increased BC without inhibiting IVP max or increasing RV in urethane-anesthetized rats. Ney et al. [23] reported that oxybutynin increased BC with increasing RV in

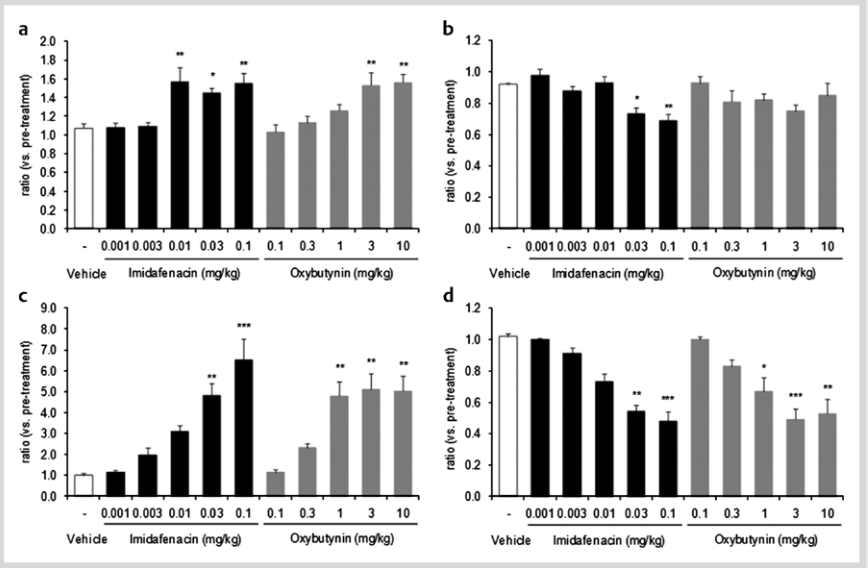

Fig. 3 Effects of imidafenacin and oxybutynin on bladder capacity **a**, maximum intravesical pressure **b**, residual urine volume **c**, and voiding efficiency **d** in urethane-anesthetized rats. Vehicle, imidafenacin and oxybutynin were administered intravenously. Data are expressed as a ratio of post- to pre-treatment value. Each column and bar represents the mean ± standard error of the mean of 5 animals. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. vehicle group (Dunnett's multiple comparison test). *Oxybutynin;* oxybutynin chloride.

conscious rats. These findings are in agreement with our present results. To our knowledge, however, there have been no studies reported so far from viewpoint of uroflowmetric indices such as Qmax, which reflects more directly the voiding function for comparative evaluation of the effectiveness among antimuscarinics. Probably, the present study is the first to investigate the risk of voiding dysfunction of antimuscarinics using such as uroflowmetric index.

Imidafenacin and oxybutynin decreased Qmax dose-dependently (**Fig. 2a**). Moreover, imidafenacin did not affect Qmax at the minimum dose of increasing BC, whereas oxybutynin affected Qmax at such a minimum dose (**Fig. 2a**). These results suggest that the relative risk of potentially inducing the voiding dysfunction is lower in imidafenacin than in oxybutynin. One of the reasons for this difference is that imidafenacin may act more selectively on bladder afferent pathway than detrusor muscle, when compared with oxybutynin. Indeed, in urethane-anesthetized rats of this study, imidafenacin did not affect IVPmax, RV, and VE at the minimum dose of increasing BC, but oxybutynin affected RV and VE at the dose levels lower than the minimum dose of increasing BC (**Fig. 3b,c,d**). Similar results have been reported using urethane-anesthetized rats and cerebral infarction rats [11,13,24]. As one of putative mechanisms behind these, Yamada et al. [25] indicated that imidafenacin excreted in urine may contribute to its selective and long-lasting distribution in the bladder, because imidafenacin showed a significant binding to bladder muscarinic receptors in rats following intravesical injection at concentration levels similar to its urine concentrations after oral administration in rats as well as healthy volunteers. Mansfield [26] suggested that antimuscarinic drugs excreted in urine may have therapeutic potential. The urinary excretion rate (percentage of doses) of oxybutynine in humans is less than 5% [26]. On the other hand, the urinary excretion rate of imidafenacin in humans is relatively high (7.8%) [27]. Because any antimuscarinic drug excreted in the urine may have direct access to urothelial muscarinic receptors [28], antimuscarinic drugs excreted in the urine have the potential enough to act on afferent nerve more easily than on detrusor muscle. Therefore, the above difference in excretion rates between imidafenacin and oxybutynin may produce differences in the relative influence index found in the present study. Another probable reason is that oxybutynin has a stronger inhibitory effect on detrusor contractility than imidafenacin because of the former's Ca^{2+} channel antagonist actions [29].

Table 1 The minimum doses of decreasing the maximum urinary flow rate (Qmax) and increasing the bladder capacity (BC).

Drug	Minimum effective dose		Ratio (C)
	Qmax (A)	BC (B)	
Imidafenacin	0.03	0.01	3
Oxybutynin	1	3	0.3

The dose ratio (C) was calculated by dividing the minimum dose (A) of decreasing Qmax by that (B) of increasing BC
Oxybutynin; oxybutynin chloride

Imidafenacin has a greater ratio of the minimum influence dose in decreasing Qmax to the minimum influence dose in increasing BC than oxybutynin (**Table 1**). In some clinical studies, urinary retention has been reported in patients with OAB during oxybutynin treatment [19,30]. On the other hand, no urinary retention has been reported in patients with OAB during imidafenacin treatment [14]. Furthermore, combination therapy of imidafenacin with tamsulosin in BPH patients induced no urinary retention in any of the patients in the ADDITION study, unlike other antimuscarinics [18]. Considering these clinical reports, imidafenacin may have less influence on voiding function than oxybutynin. But since these clinical studies were performed under limited conditions, such as defined study period and selected patients with a certain baseline severity, it is still unclear whether imidafenacin actually has less risk of inducing AUR compared with other antimuscarinics. The present study with rats, however, shows that antimuscarinics may have varying degrees of impact on voiding difficulty. The present authors, therefore, are very interested in whether imidafenacin actually has little influence on risk of AUR in BPH patients during its long term administration or in those with a severe condition. In addition, this study suggests that new generation antimuscarinic imidafenacin is considered more beneficial than first-generation antimuscarinic oxybutynin, and thus the authors are also interested in whether new generation of antimuscarinics are different in their clinical benefit. As the first step, it is intriguing challenges to compare influences on voiding function among the

new generation of antimuscarinics, and furthermore, to investigate whether the receptor selectivity is related to the difference in the influence on voiding function in animal models of BPH.
In conclusion, this study demonstrated that imidafenacin has a lower relative risk of voiding difficulty than oxybutynin in comparing the relative effects of these 2 antimuscarinics on the Qmax obtained from rats with functional urethral obstruction and on the bladder capacity obtained from the urethane-anesthetized rats. These results provide new information that antimuscarinics may have varying degrees of impact on voiding difficulty. Thus, more comparative studies will be needed to further clarify such differences in degrees of impact on the voiding phase among more antimuscarinic drugs.

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Conflict of Interest

All authors are employees of Kyorin Pharmaceutical Co., Ltd. The company funded and approved the conduct of the study. The authors conducted the study at their own discretion and have editorial freedom with respect to the manuscript. The authors will not receive any monetary reward from the company even after the manuscript is accepted. The authors are currently applying for a patent on the evaluation method of the present study. The patent application (Application number: JP2013-164181) is pending.

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