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Bladder Selectivity of Imidafenacin, a Novel Antimuscarinic Agent Developed to Treat Overactive Bladder

Shizuo Yamada[1], Akira Yoshida[1], Masaki Ogoda[1], Yusuke Fuchihata[1], Shiori Kuraoka[1], Hideo Tsukada[2] and Tsuyoshi Anraku[3]

[1] Department of Pharmacokinetics and Pharmacodynamics and Global Center of Excellence (COE) Program, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan; [2] Central Research Laboratory, Hamamatsu Photonics KK, Shizuoka 434-8601, Japan and [3]Development Research Laboratories, Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan

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Abstract

Imidafenacin, a potent M_1 and M_3-subtype selective antagonist, is now used clinically in Japan for the treatment of overactive bladder (OAB). Pharmacological studies of this agent showed selectivity in the bladder over salivary gland and brain. The oral administration of imidafenacin at low doses caused a more selective and longer-lasting binding to muscarinic receptors in the bladder than at other tissues such as the salivary gland, heart, colon, lung and brain, suggesting preferential muscarinic receptor binding in the bladder. Pharmacokinetic data showed that the orally administered imidafenacin distributed at a higher concentration in the bladder compared to that in the serum or submaxillary gland of rats. Furthermore, a significant level of imidafenacin was detected in the urine of rats treated orally with this agent. The intravesical instillation of imidafenacin resulted in significant binding of bladder muscarinic receptors. In experiments using autoradiography (ARG) and positron emission tomography (PET), imidafenacin exerted little significant binding of muscarinic receptors in rat brain and no impairment of cognitive behavior in rats and monkeys. Clinical studies indicated a favorable efficacy-to-side effect ratio of imidafenacin in patients with OAB. Thus, imidafenacin when given orally exhibits predominant distribution to the bladder and possibly exerting a more selective and persistent pharmacological effect on the bladder than other tissues including the submaxillary gland, colon and brain. Such selectivity may be attributable to a direct blockade of bladder muscarinic receptors by the excreted urinary imidafenacin. Thus, imidafenacin may be efficacious in treating patients with an overactive bladder, with the improved tolerability beyond the currently available agents.

Keywords: Overactive bladder; Bladder selectivity; Muscarinic receptor binding; *In vivo* receptor binding; Positron emission tomography, Clinical effects

Introduction

Lower urinary tract symptoms (LUTS), characterized by an increased frequency of micturition, urgency, urge incontinence and urinary obstruction, are very common in the geriatric population, a group that is rapidly increasing in number (1-3). Muscarinic receptor antagonists are widely used as first-line therapy for LUTS due to benign prostatic hyperplasia (BPH) and overactive bladder (OAB) (4, 5). While these antagonists have proven effective in patients with OAB, they are also associated with anticholinergic side effects including dry mouth, constipation, somnolence and blurred vision, because the muscarinic receptor mediates the excitatory and inhibitory actions of acetylcholine in the central and peripheral nervous systems (4). Dry

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Correspondence: Department of Pharmacokinetics and Pharmacodynamics and Global Center of Excellence (COE) Program, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan. Fax: +81-54-264-5635. email: yamada@u-shizuoka-ken.ac.jp

mouth is the most common of these complaints and decreases quality of life. Therefore, numerous studies involving muscarinic receptor antagonists to treat OAB have focused on targeting the urinary bladder over the salivary gland. The side effects on the central nervous system (CNS) generally occur at a lower frequency than dry mouth, but may be of great concern in elderly patients because of an increase in blood-brain barrier (BBB) permeability with aging (5, 6). In this connection, clinical studies demonstrate increased cognitive sensitivity to scopolamine (7, 8) and a reduced density of brain muscarinic receptors in the elderly (9). So, it is important to evaluate the bladder selectivity of muscarinic receptor antagonists used to treat OAB for optimal medication.

Imidafenacin (KRP-197/ONO-8025), 4-(2-Methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide (Fig. 1), a novel antimuscarinic drug with high tissue selectivity (organ specificity) for urinary bladder, was approved for treating overactive bladder in Japan in 2007. This review article focuses on the bladder selectivity of imidafenacin in terms of pharmacological effects and muscarinic receptor binding.

Pharmacological profiles of imidafenacin

Analysis of subtype-selectivity using recombinant human muscarinic receptors demonstrated that imidafenacin exerted higher affinity for the M_1 and M_3 than M_2 subtype, with Ki values in the low nM range (10). Similar high potency and high selectivity for M_1 and M_3 over the M_2 subtype were obtained in the *in vitro* functional antagonism assays using isolated animal organs, while major metabolites of this drug in humans had no effect on overall antimuscarinic activity under the same experimental conditions (10). These functional assays also revealed that imidafenacin inhibited not only the contraction of detrusor muscle but also the release of acetylcholine from parasympathetic nerve terminals in the bladder, which were mainly mediated by antagonistic actions against M_3 and M_1 receptors, respectively (10). These results suggest that imidafenacin has an advantage in the effective inhibition of detrusor contraction over pure M3 antagonists. In the evaluation of urinary bladder function *in vivo*, intragastric administration of imidafenacin to rats resulted in a dose-dependent suppression of the carbachol-induced decrease in bladder capacity, with an ID_{50} value of 0.055 mg/kg (11). Additionally this drug was more effective in inhibiting distention-induced rhythmic bladder contractions in rats, than some currently marketed antimuscarinic drugs, oxybutynin, propiverine, tolterodine and darifenacin (11). The resultant selectivity of imidafenacin for the bladder over salivary gland, based on the inhibitory effect on rhythmic bladder contraction and carbachol-induced salivary secretion, was superior to that of all other antimuscarinic drugs tested (Table 1) (11).

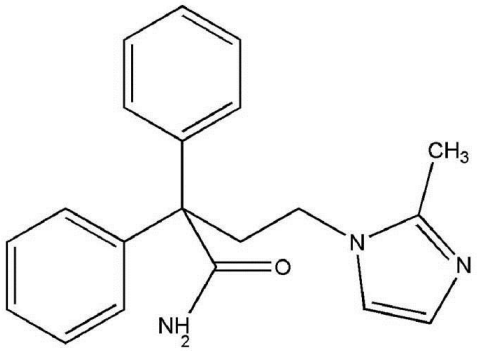

Figure 1. Chemical structure of imidafenacin.

Muscarinic receptor binding in the bladder and pharmacokinetics

The comparative analysis of muscarinic receptor binding characteristics in the lower urinary tract and other tissues after the systemic administration of therapeutic agents allows the rationale for their pharmacological characteristics from the integrated viewpoint of pharmacokinetics and pharmacodynamics (12, 13). The effects of orally administered imidafenacin on the binding of muscarinic receptors in rat tissues were characterized in relation to the drug's pharmacokinetics. In the experiments *in vitro,* imidafenacin competed in a concentration-dependent manner with [^{11}C]NMS for binding sites in the bladder, submaxillary gland, colon, lung, and brain, with a potency equal to or greater that of oxybutynin (14). Also, the affinity of imidafenacin for muscarinic receptors was significantly lower in the bladder than submaxillary gland or colon, while it was significantly greater than that in the heart. Greater affinity of

Table 1. Selectivity of imidafenacin and some currently marketed antimuscarinic drugs for bladder over salivary gland in conscious rats.

Drug	Rhythmic bladder contraction ID_{30} (mg/kg,i.g.)	Salivary secretion ID_{50} (mg/kg,i.g.)	Relative bladder selectivity
Imidafenacin	0.17	1.5	8.8
Propiverine	15	14	0.9
Tolterodine	3.0	15	5.0
Oxybutynin	3.2	4.4	1.4
Darifenacin	0.85	1.2	1.4

Muscarinic receptors are involved in approximately 60% of distention-induced bladder rhythmic contractions, and therefore the ID_{30} value was assumed to correspond to approximately the half-inhibitory dose (ID_{50} value). Bladder selectivity was expressed as the ratio between potency for distention-induced rhythmic bladder contraction and for carbachol-induced salivary secretion. Modified with permission from Kobayashi et al. (11).

imidafenacin for muscarinic receptors in the exocrine gland than bladder was also observed in human tissues (15). Since imidafenacin exhibited greater selectivity for the M_3 than M_2 subtype (10), the high affinity of this drug for muscarinic receptors in the rat submaxillary gland reflects M_3 subtype selectivity.

Following the oral administration of imidafenacin (0.25-2.0 mg/kg), there were dose- and time-dependent muscarinic receptor binding in the bladder, submaxillary gland, heart, colon, and lung but not brain of rats (14). The receptor binding by imidafenacin at 0.25 and 0.5 mg/kg was observed only in the bladder and submaxillary gland, and was rapid in onset and relatively longer-lasting in the bladder (Fig. 2B). The results demonstrate that orally administered imidafenacin binds muscarinic receptors more selectively in the bladder than in other tissues.

In the pharmacokinetic study in rats, the orally administered imidafenacin was distributed more to the bladder and submaxillary gland than the serum, and the tissue concentration was much higher in the bladder than the submaxillary gland (14) (Fig. 2A). The imidafenacin concentration in the colon was markedly low. The specific distribution of imidafenacin to the bladder might be related to its significant excretion into the urine. Up to 48 h after the oral administration of imidafenacin (0.1 mg) in healthy volunteers, approximately 7.3% of the dose was excreted into urine as the parent compound and the maximum concentration was 293 nM (16). A similar concentration (approximately 200 nM) of imidafenacin was excreted in the urine of rats that received this agent at a dose of 0.5 mg/kg. In fact, significant binding of bladder muscarinic receptors was observed on the intravesical instillation of imidafenacin at concentrations of 30-3000 nM. Taken together, these results suggest that some imidafenacin is transferred directly from urine to the bladder tissue by simple diffusion, and thus this agent could contribute greatly to the selective and long-lasting binding of bladder muscarinic receptors in rats. It can therefore be presumed that the significant binding of bladder muscarinic receptors by the excreted urinary imidafenacin is pharmacologically relevant in terms of the functional blockade of these receptors (Fig. 3).

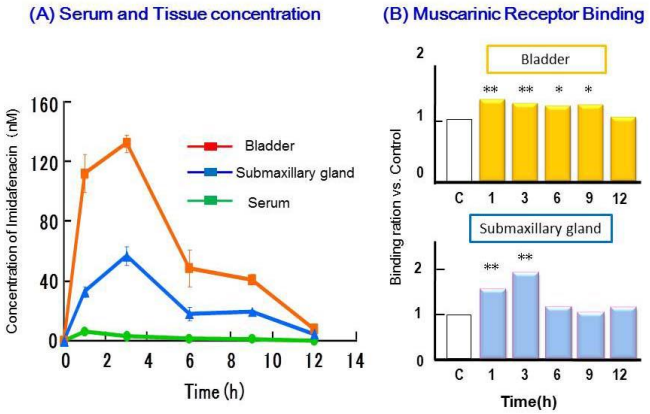

Figure 2. Serum and tissue (bladder, submaxillary gland) concentrations of imidafenacin (A) and muscarinic receptor binding activity (increase in the dissociation constant (K_d) for specific [^{3}H]NMS binding) in the bladder and submaxillary gland (B) of rats at 1-12 h after the oral administration of imidafenacin (2.0 mg: 6.26 μmol/kg). Significantly different from the control value (C), *P<0.05, **P<0.01.

Muscarinic receptor binding in the brain

Muscarinic receptors play important roles in numerous physiological functions including higher cognitive processes such as memory and learning (17).

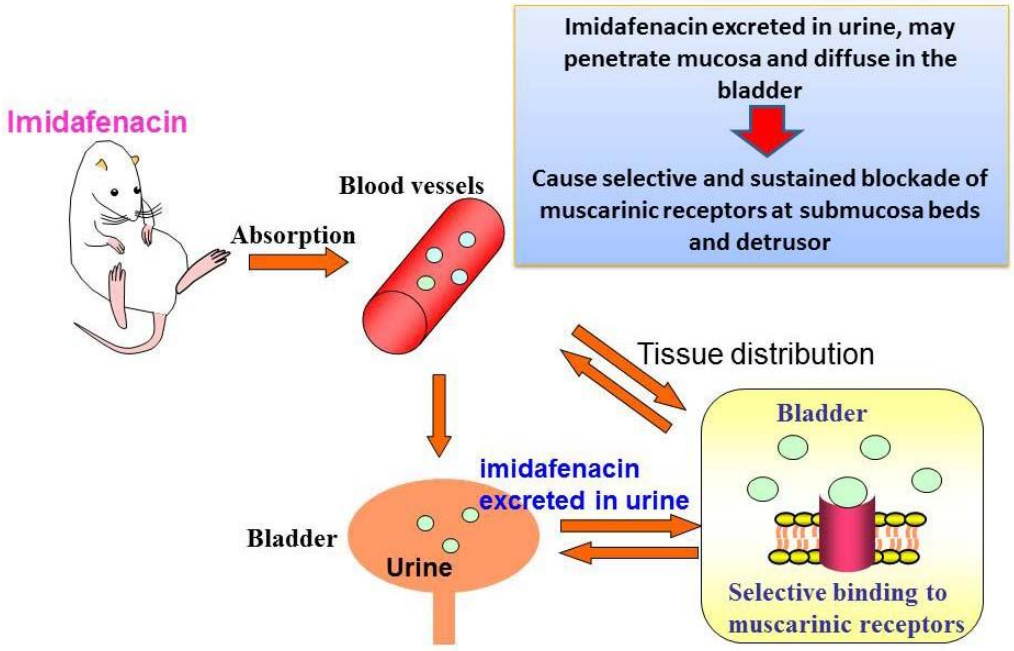

Figure 3. Possible mechanism for the bladder selectivity of imidafenacin. Imidafenacin administered orally is absorbed into the blood, and then distributed to the bladder tissue. Also, some imidafenacin excreted into the urine is distributed into the bladder. The distributed imidafenacin may bind to the muscarinic receptors in the submucosal beds (urothelium etc) and detrusors.

Deterioration in cognitive function during treatment with antimuscarinic drugs for overactive bladder is of growing concern, particularly in elderly and dementia patients. In fact, oxybutynin and tolterodine have been associated with cognitive adverse events (18, 19).

It was shown that oral administration of imidafenacin at doses of 0.25, 0.5 and 2.0 mg/kg (0.79, 1.57 and 6.26 μmol/kg, respectively) had little effect on muscarinic receptor binding parameters in the rat brain while oxybutynin bound significantly to muscarinic receptors (14). The *in vivo* imaging of brain receptors by autoradiography (ARG) and positron emission tomography (PET) allows the precise localization of muscarinic receptors and the pharmacological characterization of muscarinic receptor antagonists (20, 21). Yoshida et al (22) characterized noninvasively muscarinic receptor occupancy in the rat brain after the systemic injection of imidafanacin, oxybutynin and darifenacin by PET, comparing the results with those of *in vivo* ARG and *ex vivo* radioreceptor assays. In the PET study using rats, the intravenous injection of oxybutynin but not imidafenacin or darifenacin at pharmacological doses decreased the binding potential of (+)*N*-[^{11}C]methyl-3-piperidyl benzilate ([^{3}H](+)33-MPB), a PET ligand of muscarinic receptor, in the cerebral cortex and corpus striatum in a dose-dependent manner (Fig. 4) (22). Similarly, in the receptor ARG analysis, oxybutynin dose-dependently decreased the binding of [^{11}C](+)3-MPB in each region of the brain, whereas imidafenacin and darifenacin had little effect (21, 22).

The effects of imidafenacin and oxybutynin on the central muscarinic receptors and cognitive function in conscious monkeys were investigated (23). The occupancy levels of central muscarinic receptors and cognitive function were assessed with [^{11}C](+)3-MPB-PET measurements and the T–DMS task, respectively, in the same animals. Oxybutynin (0.1-1.0 mg/kg) administered orally occupied muscarinic receptors dose-dependently 1 hr post-administration, and cognitive function was significantly impaired in a dose-dependent manner at doses of 0.3 and 1.0 mg/kg. Imidafenacin (0.01-0.1 mg/kg, p.o.) also occupied muscarinic receptors to some extent, but did not induce cognitive impairment at all. This is consistent with pharmacological data showing that imidafenacin did not affect escape latency in the Morris water maze task in rats (spatial learning and memory) (11) and with clinical data showing that this agent was well-tolerated with fewer adverse effects (24-27).

The muscarinic receptor binding and behavioral observations may be based on little occupancy of brain muscarinic receptors possibly due to the low permeability of the blood-brain barrier (BBB). Muscarinic receptor antagonists must first cross the BBB to distribute into the brain and to occupy the CNS receptors. The observed difference among muscarinic receptor antagonists in the degree of uptake and binding to muscarinic receptors in the brain may depend on their ability to permeate the BBB. The passive penetration of the BBB is dependent principally on physicochemical properties (28), and thus its small size and molecular characteristics (high lipophilicity and neutral polarity) make oxybutynin likely to cross the BBB. In contrast, both imidafenacin and darifenacin have moderate polarity and low lipophilicity, suggestive of lower permeability. In addition, darifenacin is considered a substrate of P-glycoprotein, an active-transport system that carries this agent back across the BBB (29).

Clinical efficacy, safety and tolerability of imidafenacin

A large randomized controlled trial of 12 weeks' treatment with imidafenacin for patients with an overactive bladder has provided evidence that this drug was not inferior to propiverine for the improvement of incontinence, was well tolerated, and had significantly lower incidence of adverse events than propiverine (25). Moreover, in the treatment of imidafenacin for 52 weeks, the long term safety and efficacy of this drug has been demonstrated in patients with overactive bladder (24). Thus imidafenacin has a favorable balance of clinical efficacy in treating overactive bladder together with a reduced risk of adverse effects.

Conclusions

Imidafenacin exerts a selective pharmacological effect on the bladder. Imidafenacin, when given orally, distributes mostly to the bladder where it exhibits more selectivity and persisting effect when compared to its effect on other tissues including the submaxillary gland, colon and brain (14). The indicated selectivity may occur due to a direct blockade of bladder muscarinic receptors by imidafenacin excreted in the urine (14). Therefore, compared to oxybutynin, imidafenacin may be more efficacious to treat patients with an overactive bladder (14).

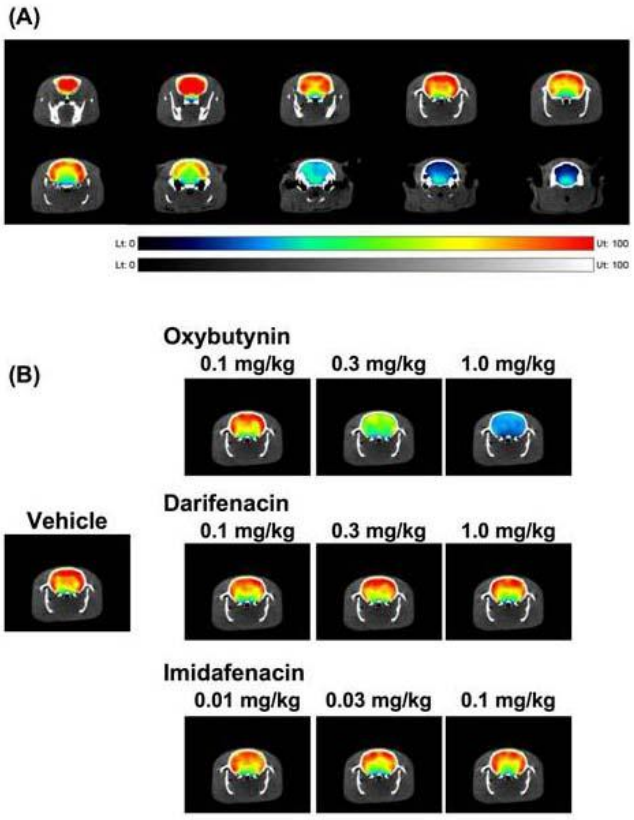

Figure 4. (A) Typical PET images fused with CT images in the brain regions of rats received i.v. injection of [^{11}C](+)3-MPB. The images were generated by summation of image data from 40-60 min after [^{11}C](+)3-MPB injection. Each coronal section was different at 2.1 mm intervals. Upper left section: frontal lobe region, lower right section: cerebellum region. Third section in the upper panel was Bregma. **(B) Effects of different doses of oxybutynin, darifenacin and imidafenacin on PET images of [^{11}C](+)3-MPB in the rat brain.** Rats were received i.v. injection of agents 10 min prior to the [^{11}C](+)3-MPB injection. Each section represents the typical one of Bregma – 2.1 mm region (fourth section in the upper panel (A)). This modified figure was reproduced from Ref. 22 with permission.

Conflicts of Interest

No potential conflicts of interest to disclose.

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