The Design and Development of Fesoterodine as a Prodrug of 5-Hydroxymethyl Tolterodine (5-HMT), the Active Metabolite of Tolterodine

B. Malhotra*[,1], K. Gandelman[1], R. Sachse[2], N. Wood[3], M.C. Michel[4]

[1]*Pfizer Inc, New York, NY, USA;* [2]*SCHWARZ BioSciences, Monheim, Germany;* [3]*Pfizer Global Research and Development, Sandwich, Kent, UK;* [4]*University of Amsterdam, Amsterdam, The Netherlands*

Abstract: This review highlights the design and development of fesoterodine **(Toviaz®)** as a prodrug of 5-hydroxymethyl tolterodine (5-HMT), which is also the active metabolite of tolterodine, for the treatment of overactive bladder (OAB). Tolterodine and 5-HMT are both potent antimuscarinic agents. A prodrug approach was necessary for systemic bioavailability of 5-HMT after oral administration. Fesoterodine was selected amongst a series of ester analogues of 5-HMT to develop an advanced OAB treatment with an optimum biopharmaceutics profile, while maintaining a pharmacological link to tolterodine.

While tolterodine and 5-HMT have similar antimuscarinic activity, the logD value, a determinant of lipophilicity and permeability across biological interfaces such as the gut wall and blood-brain barrier, is considerably lower for 5-HMT (0.74) versus tolterodine (1.83). In contrast to the cytochrome P450 (CYP) 2D6-mediated metabolism of tolterodine, 5-HMT formation from fesoterodine occurs *via* ubiquitous nonspecific esterases. Consequently, treatment with fesoterodine results in consistent, genotype-independent exposure to a singular active moiety (5-HMT); treatment with tolterodine results in CYP2D6 genotype-dependent exposure to varying proportions of two active moieties (5-HMT and tolterodine). At least partially due to the avoidance of variations in pharmacokinetic exposures observed with tolterodine, it was possible to develop fesoterodine with the flexibility of two efficacious and well-tolerated dosage regimens of 4 and 8 mg daily.

Keywords: Fesoterodine, prodrug, 5-HMT, tolterodine, metabolite, lipophilicity, CNS.

INTRODUCTION

Overactive bladder (OAB) is defined by the International Continence Society as urgency, with or without urgency incontinence, usually accompanied by increased daytime frequency and nocturia [1]. The etiology of OAB remains unclear, although it is generally accepted that OAB is often associated with detrusor overactivity, which may result from inappropriate levels of cholinergic activation of muscarinic receptors on the detrusor muscle or afferent nerves [2]. Antimuscarinic agents are the mainstay of pharmacologic treatment for OAB; their therapeutic effect is presumably mediated *via* blockade of muscarinic receptors on detrusor smooth muscle cells, urothelium, and/or sensory afferents, thereby inhibiting detrusor contractions [3, 4].

Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium are among the antimuscarinic drugs approved for the treatment of urgency urinary incontinence (UUI) and other symptoms related to OAB. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment [5-7]. Tolterodine, a potent and competitive antimuscarinic agent, was the first drug specifically developed for OAB treatment. Preclinical pharmacological data show that tolterodine exhibits more potent antimuscarinic receptor activity *in vivo* in the urinary bladder over the effect on the salivation, whereas oxybutynin exhibits the reverse selectivity [8]. The favorable bladder selectivity of tolterodine demonstrated in preclinical studies has been confirmed in clinical studies [6]. Tolterodine being a tertiary amine, combined with other physicochemical attributes such as low lipophilicity and positive charge, has relatively low central nervous system (CNS) penetration in animal models and a low incidence of CNS adverse events in clinical trials [9-11]. Thus good clinical efficacy combined with low incidences of dry mouth and other antimuscarinic side effects makes tolterodine a treatment of choice for OAB [12, 13]. However, clinicians and patients are not completely satisfied with OAB therapy despite the availability of tolterodine and the newer antimuscarinic agents, solifenacin and darifenacin, because of a suboptimal efficacy/tolerability balance or the inability to achieve optimal efficacy in difficult-to-treat patients.

The clinical effects of tolterodine are derived from the combined exposure to two active moieties, the parent drug (tolterodine) and its equipotent active metabolite (5-hydroxymethyl tolterodine; 5-HMT), which is formed *via* a major pathway involving the cytochrome P450 (CYP) 2D6 enzyme [14]. Since CYP2D6 is genetically polymorphic there is considerable variability among patients in the proportion of these moieties, with higher exposures to tolterodine in CYP2D6 poor metabolizers (PMs) compared with extensive metabolizers (EMs) [14, 15]. In a multiple-dose study of tolterodine, the tolterodine area under the concentration-time curve (AUC) values varied over a 130-fold range across CYP2D6 EMs and PMs whereas those for 5-HMT varied over a 5-fold range in EMs (5-HMT was not formed in PMs) [15]. Likely due to the high variability of tolterodine exposures, the development of tolterodine was limited to only a single dosage of 4 mg daily, although the dose may be lowered to 2 mg daily based on individual response and tolerability.

Delivery of 5-HMT as a new drug without involving CYP2D6-mediated metabolism of tolterodine has advantages compared to tolterodine because only one active principle would be handled by the patients with less variability, which

*Address correspondence to this author at the Clinical Sciences, Pfizer Inc, 685 3rd Avenue, New York, NY 10017, USA; Tel: 1-212-733-4723; Fax: 1-212-441-4490; E-mail: bimal.k.malhotra@pfizer.com

0929-8673/09 $55.00+.00

should result in a lower variation in efficacy and fewer side effects. The introduction of an additional hydroxyl group in the tolterodine molecule, however, results in reduced lipophilicity, which could produce a side effect profile with CNS penetration even lower than that of tolterodine but would also result in lower absorption/bioavailability. In order to overcome the absorption disadvantage, different prodrugs of 5-HMT have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes, and enzymatic cleavage.

Fesoterodine **(Toviaz®)** is the isobutyric acid ester of 5-HMT which, based on its optimum biopharmaceutical attributes, was selected amongst a series of carboxylic acid ester analogs for development as a treatment for OAB at dosages of 4-mg and 8-mg daily. Fesoterodine is rapidly and extensively converted to 5-HMT, such that the pharmacologic activity appears to be primarily attributable to 5-HMT [16, 17]. The physicochemical, pharmacologic, and metabolic properties of fesoterodine, in relation to tolterodine, and the rationale for the development of fesoterodine are the subject of this review.

1. Antimuscarinic Pharmacology of Tolterodine and 5-HMT

The antimuscarinic activities of fesoterodine, tolterodine and 5-HMT have been evaluated in membrane preparations of Chinese hamster ovary cells expressing the five muscarinic receptor subtypes (M_1–M_5); the functional activities were determined in organ-bath studies using the rat bladder *in vitro* and in cystometry studies in rats *in vivo* [18]. These studies demonstrated that 5-HMT is the main active principle of fesoterodine, which acts as a prodrug, and that both tolterodine and 5-HMT are specific muscarinic receptor antagonists at the M_1 through M_5 subtypes [18]. The potencies of various antimuscarinic agents, expressed as Ki values for each muscarinic receptor subtype, are summarized in Table **1** [19-24]. Across different studies reported in the literature, the absolute values of the *in vitro* affinity estimates vary somewhat, however, the relative affinities for the receptor subtypes are consistent for each antimuscarinic drug. Fesoterodine, being a prodrug, has very low but similar affinity across the five muscarinic receptor subtypes.

2. Biopharmaceutics and Preclinical Pharmacologic Assessment: Selection of Fesoterodine

A comprehensive evaluation of the absorption, distribution, metabolism, and excretion (ADME) properties in preclinical models and in Phase 1 clinical pharmacology studies forms the biopharmaceutics-related determination of the development potential of therapeutic drug molecules. An integration of the knowledge of the biopharmaceutics and preclinical pharmacological properties of a drug along with anatomic distribution of receptors can become useful in a qualitative prediction of the beneficial and adverse effects of the drug.

Lipophilicity and CNS Penetration of 5-HMT

Muscarinic receptors are not only located in the target organ responsible for efficacy (bladder) but also in other tissues and organs (gastrointestinal tract, salivary glands, heart, and brain) that can affect the tolerability and safety of an antimuscarinic drug. For example, antimuscarinic drugs with greater M_3 receptor occupation may cause greater incidence of dry mouth and constipation [25]. Relevant to the antimuscarinic pharmacology in the CNS, physicochemical properties such as lipophilicity and permeability are important predictors of the ability of a molecule to penetrate the blood-brain barrier (BBB), such that those with higher lipophilicity at physiologic pH are more likely to exert pharmacologic adverse effects (AEs) in the CNS. The logD values at the physiologic pH 7.4, determined from the octanol:water distribution coefficient [26], are commonly used to compare the lipophilicity of drugs as an indicator of their ability to cross the BBB and their propensity to cause CNS AEs. A significant and positive correlation between logD and CNS AEs has been demonstrated across the class of triptan drugs for the treatment of migraines [27].

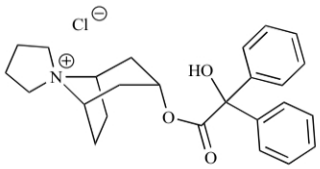
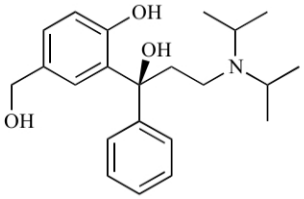
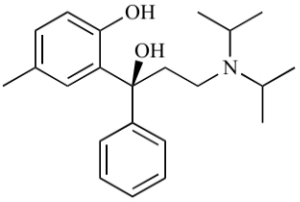
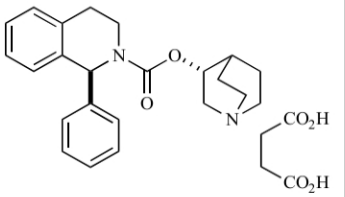
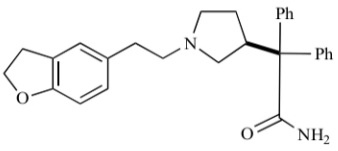
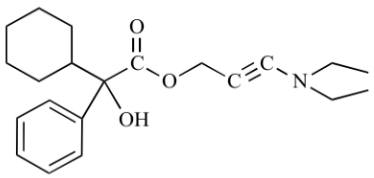
The logD for 5-HMT [14], tolterodine [14], and other antimuscarinic agents [14, 28-30] is shown in Table **2**. 5-HMT has demonstrated low lipophilicity at acidic pH and higher lipophilicity at more basic pH [31], as expected for a compound with a pKa value of 9.28. The logD values of tolterodine and 5-HMT have been reported to be 1.83 and 0.74, respectively (Table **2**) [14]. In addition, the lipophilicity of several antimuscarinic agents used for treatment of OAB has been reported previously [14, 29, 32, 33]. Tolterodine has low lipophilicity and low CNS penetration (brain/blood ratio, 0.1–0.3 for radioactivity) in mice [14] with no significant CNS AEs observed in patients [34]. LogD values for solifenacin and oxybutynin are reported to be 1.69 and >3.3, respectively, suggesting that both of these compounds are more lipophilic than 5-HMT (Table **2**) [24, 35]. Trospium chloride is a quaternary ammonium compound and, as such, would not cross the BBB because of its low lipophilicity (Table **2**) [32]. The small logD for 5-HMT suggests that it is

Table 1. Affinity of Various Antimuscarinic Drugs for Human Muscarinic Receptor Subtypes

Muscarinic Receptor Subtype	Ki, nM						
	Tolterodine [21, 22, 24]	5-HMT [21, 22]	Fesoterodine [22]	Trospium [23]	Solifenacin [24]	Darifenacin [19, 24]	Oxybutynin [22, 24]
M_1	3.0, 3.0, 2.7	2.3, 1.8	624	0.8	26	35, 31	2.4, 6.1
M_2	3.8, 6.4, 4.2	2.0, 1.7	566	0.6	170	56, 100	6.7, 21
M_3	3.4, 12, 4.4	2.5, 6.3	ND	0.5	12	1.2, 2.0	0.67, 3.4
M_4	5.0, 1.9, 6.6	2.8, 1.0	177	1.0	110	18, 52	2.0, 6.6
M_5	3.4, 4.6, 2.5	2.9, 5.2	ND	1.9	31	9.0, 8.2	11, 18

ND: Not Determinable (<50% binding at 1 μM).

Table 2. Lipophilicity of Various Antimuscarinic Agents for Overactive Bladder

Antimuscarinic Agent LogD	**Trospium -1.22 [28]**	**5-HMT 0.74 [14]**	**Tolterodine 1.83 [14]**
			
Antimuscarinic Agent LogD	**Solifenacin 1.69 [29]**	**Darifenacin 2.7 [30]**	**Oxybutynin >3.3 [14]**
			

unlikely to cross the BBB and cause CNS effects. The low CNS penetration potential of 5-HMT is of particular clinical relevance in elderly patients, who may be taking a number of concomitant medications and are vulnerable to CNS AEs.

A study comparing changes in quantitative-topographical electroencephalogram (qEEG) activity following administration of antimuscarinic agents demonstrated that oxybutynin, a tertiary amine, caused significant changes in four frequency bands compared with placebo and produced the highest number of CNS-related effects [34]. Neither tolterodine, also a tertiary amine, or trospium chloride, a quarternary amine, produced significant changes in qEEG activity compared with placebo.

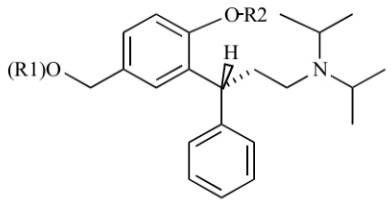
The brain/plasma ratios of fesoterodine-related radioactivity have been reported to be approximately 0.04 and 0.07 for maximal drug concentration (C_{max}) and AUC, respectively, after single oral doses of ^{14}C-fesoterodine given to mice (data on file, Pfizer Inc). Similarly, permeability studies in a porcine model demonstrated that the BBB permeability coefficient of 5-HMT is 6.5×10^{-6} cm/s compared with permeability coefficients of 23×10^{-6} cm/s for oxybutynin, solifenacin, and darifenacin (data on file: Pfizer Inc). Lower brain/plasma ratio and permeability with fesoterodine compared with tolterodine suggest an even lower risk of CNS AEs with fesoterodine than with tolterodine. In Phase 3 clinical trials with fesoterodine, following once-daily administration of fesoterodine 4 or 8 mg or tolterodine 4 mg, there were no CNS AEs with an incidence rate greater than 2% or exceeding that following placebo administration [9, 10, 36, 37]. Similarly, in a Phase 3 study of tolterodine, the incidence of CNS AEs of somnolence and dizziness was low (3% and 2%, respectively) but slightly higher than that for placebo (2% and 1%, respectively) [38].

Permeability of 5-HMT: Improving Absorbability by Prodrug Approach

While the lower lipophilicity of 5-HMT favors its CNS tolerability through lower CNS penetration, it also affects the ability of 5-HMT to permeate other biological barriers, such as gut wall or skin for oral or transdermal delivery, respectively. Therefore, a prodrug approach was considered to structurally modify 5-HMT for enhanced permeability across human skin to facilitate the delivery of 5-HMT into the systemic circulation. Ester derivatives were considered as the choice for developing the prodrug of 5-HMT (Table **3**), because esterases are known to be ubiquitous and are not known to be subject to genetic polymorphism or drug interactions of clinical significance [39-41]. As a result of rapid and efficient hydrolysis of an ester prodrug immediately after permeability across the gut wall or skin, only 5-HMT would be available in the systemic circulation.

To investigate the feasibility of nonsystemic delivery, the biological membrane permeability of 5-HMT along with its various ester analogues was assessed using flux rates across human skin in the flow-through cell model *in vitro* [42]. Substitution of both the hydroxy groups of 5-HMT leads to approximately a 20-fold increase in skin permeation in relation to 5-HMT. Surprisingly, monosubstitution of the phenolic hydroxy group resulted in even higher, about 50-fold increased, penetration rate through human skin. The *in vitro* metabolism of different ester prodrugs to generate the active metabolite, 5-HMT, by enzymatic process was evaluated in pooled human liver S9-preparation. The formation of the active metabolite depended on the substituents both at the benzylic and phenolic side of the respective compounds, with turnover rates ranging from 96% to 63%. Similar to permeability, monosubstitution of the phenolic hydroxy group resulted in highest turnover to form 5-HMT [42]. Overall, based on its optimized permeability (Table **3**) and

Table 3. *In Vitro* Permeability of Various Structural Analogs of 5-HMT [42]



5-HMT Ester Derivatives

R1	R2	Chemical designation (name)	Permeation Rate (μg/cm^2/24 hours)
Hydroxy	Hydroxy	HO-/-OH (5-hydroxymethyl tolterodine)	3
Hydroxy	Isobutyrate	HO-/-OBut (fesoterodine)	150
Isobutyrate	Isobutyrate	ButO-/-OBut	60
Propionate	Propionate	PropO-/-OProp	70

rapid hydrolytic conversion, the isobutyrate monoester (fesoterodine) was considered to be the best candidate for biopharmaceutical development. Furthermore, the results obtained in the receptor binding and tissue assays demonstrated that the anticholinergic activity of the compounds decreases with increased derivatization, such that the ester derivatives were significantly less potent than 5-HMT; therefore, an ester such as fesoterodine, which has optimum permeability and efficient hydrolysis, would act effectively as prodrug of 5-HMT.

3. Elimination Pathways of Tolterodine, Fesoterodine, and 5-HMT

Based on pharmacokinetic studies, it was demonstrated that fesoterodine is rapidly and extensively converted by nonspecific, ubiquitous esterases to 5-HMT, such that fesoterodine is undetectable in plasma after oral dosing [16, 17]. Furthermore, compared with 5-HMT, fesoterodine is 2 or more orders of magnitude less potent at muscarinic receptors [22]. Further biotransformation of 5-HMT results in inactive metabolites, making 5-HMT the principal active moiety of fesoterodine after oral administration [16, 17, 22] 5-HMT is also an active metabolite of tolterodine, but in contrast to fesoterodine, the metabolism of tolterodine to 5-HMT is more complex; it undergoes oxidation *via* CYP2D6 primarily in the liver (Fig. **1**) [14]. Both tolterodine and 5-HMT contribute to the pharmacologic activity observed following administration of tolterodine, but the proportion of plasma tolterodine/5-HMT varies according to a patient's CYP2D6 genotype [15, 43]. Because the CYP2D6 pathway is subject to genetic polymorphism, the efficiency with which individuals can metabolize tolterodine to 5-HMT varies across the population [44]. Overall, CYP2D6 metabolizer status can be broken down into EMs, intermediate metabolizers (IMs), or PMs [44]. Approximately 7–10% of the Caucasian population are devoid of CYP2D6 (ie, PMs) and are unable to metabolize tolterodine efficiently and do not form 5-HMT. The CYP2D6 EMs can efficiently metabolize tolterodine to 5-HMT, resulting in approximately similar exposures to tolterodine and 5-HMT. IMs are less efficient at metabolizing tolterodine, resulting in a smaller proportion of 5-HMT. This genetic variability in metabolic status, as well as variability arising from drug interactions with CYP2D6, leads to highly variable ratios of tolterodine and 5-HMT in different patients (Fig. **1**) [15, 45, 46]. As highlighted in Fig. (**1**), because fesoterodine functions as a prodrug and due to the involvement of esterases in the formation of 5-HMT, all patients are exposed to a single active moiety when fesoterodine is administered. On the contrary, tolterodine itself is also active and due to CYP2D6-mediated metabolism of tolterodine to 5-HMT, depending on patient's CYP2D6 genotype, varying proportions of two different active moieties are involved when tolterodine is administered.

Whether formed after tolterodine or fesoterodine administration, 5-HMT is subsequently metabolized to inactive carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites, with CYP2D6 and CYP3A4 identified as likely to contribute to the formation of the carboxy and the N-desisopropyl metabolites, respectively, following incubations with heterologously expressed human CYP isoforms and CYP chemical inhibitors (Fig. **2**) [20]. Thus, CYP activity appears to be responsible for the further metabolism of 5-HMT after administration of fesoterodine or tolterodine. The apparent oral clearance of 5-HMT is reduced by approximately 40% in CYP2D6 PMs compared with EMs. A similar reduction in the apparent oral clearance of 5-HMT is also noted; during concomitant administration of fesoterodine and the potent CYP3A4 inhibitor ketoconazole [47, 48]. The observation that the magnitude of the increase in 5-HMT exposure was similar when either of the 2 pathways was absent/inhibited indicates that both CYP2D6 and CYP3A4 may play equally important roles in the elimination of 5-HMT [47]. In addition to metabolic inactivation *via* two major pathways involving CYP3A4 and CYP2D6 enzymes, 5-HMT is also excreted unchanged in the urine, accounting for about 16% of the orally administered dose of fesoterodine. Because of the availability of multiple metabolic and renal pathways for the elimination of 5-HMT, patient intrinsic (hepatic or renal impairment) or extrinsic (drug interactions with potent CYP3A4 or CYP2D6 inhibitors) factors have only a modest effect of about 2.5-fold increase in 5-HMT exposures [36]. These modest increases in 5-HMT exposures

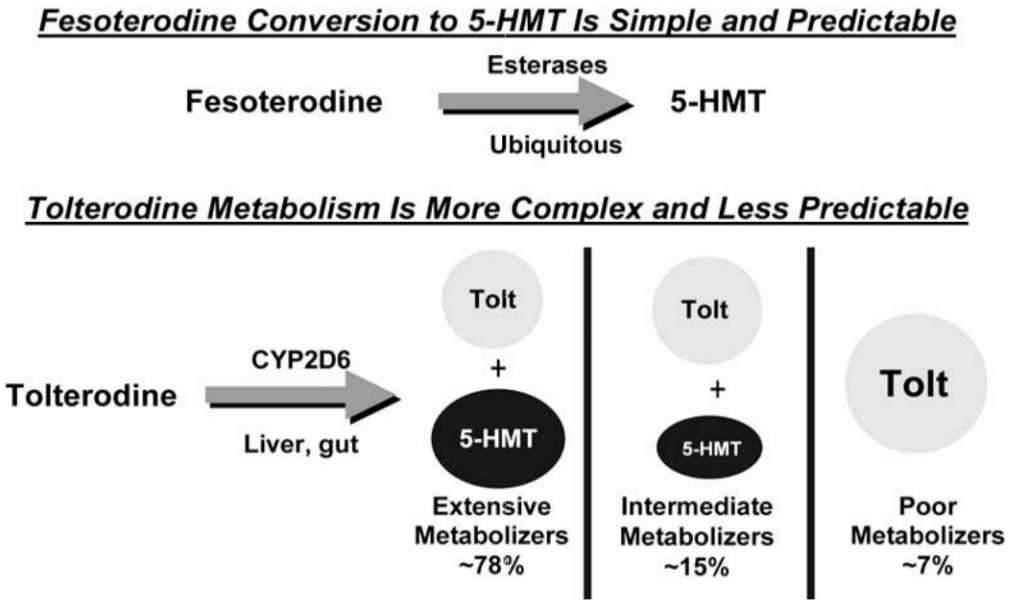


Fig. (1). Esterase-Mediated vs. CYP2D6-Mediated Formation of 5-HMT; Tolt: Tolterodine; 5-HMT: 5-hydroxymethyl tolterodine.

after fesoterodine administration are managed through simple dosing recommendations in the product label that require fesoterodine doses not exceeding the initial dose of 4 mg/day under the aforesaid situations [36]. On the other hand, since CYP2D6 is the single predominant pathway involved in the elimination of tolterodine, potent inhibition of CYP2D6 activity by fluoxetine results in marked reduction in clearance (up to 93%) and increase in exposure (up to 14-fold) of tolterodine, where as 5-HMT was undetectable [49]. Therefore, as a result of variations in patient-intrinsic and -extrinsic factors, relatively low inter-patient or inter-occasion variability in active moiety exposures is expected following fesoterodine administration compared with tolterodine.

The antimuscarinic effects of drugs used for OAB treatment [50] can potentially be attributed to the presence of M_2 and M_3 receptors (with a predominance of M_3 receptors) on the detrusor muscle and the urothelium [2]. As shown in Table **4**, some antimuscarinic agents have an appreciable urinary excretion of unchanged parent drug (trospium [51, 52] and solifenacin [53]) or an active metabolite (tolterodine [10] and fesoterodine [36]), providing exposure to the active moiety locally in the bladder. The bladder exposure to the antimuscarinic active moieties in these cases may have an effect on the afferent nerves located near the urothelium [54], which could impart additional efficacy in reducing OAB symptoms.

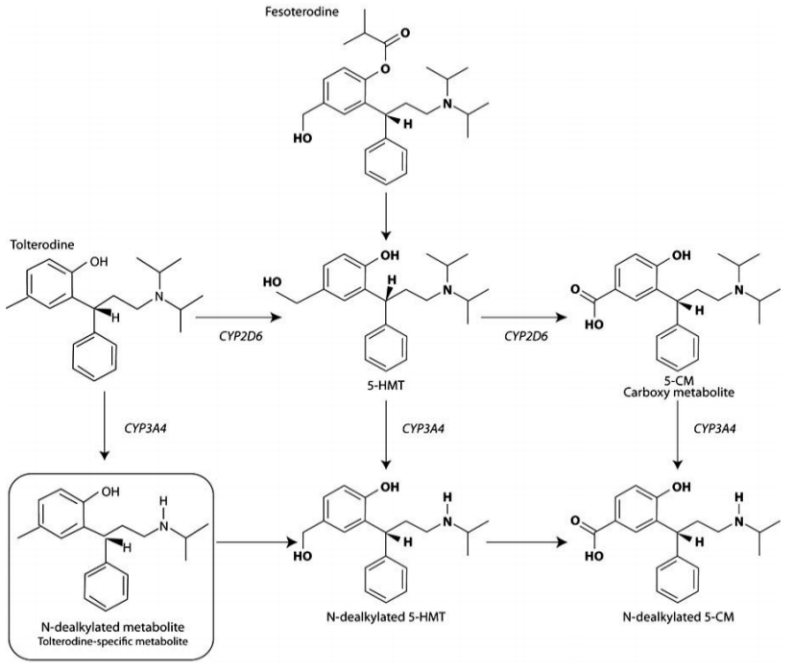


Fig. (2). Biotransformation Pathways of Fesoterodine and Tolterodine; 5-HMT: 5-hydroxymethyl tolterodine

Table 4. Systemic Bioavailability & Urinary Excretion of Various Antimuscarinic Drugs for Overactive Bladder

Trade Name (generic name)	Toviaz® [36] (fesoterodine)	Detrol LA® [10] (tolterodine)		Sanctura® [51] (trospium)	Sanctura® XR [52] (trospium)	Vesicare® [53] (solifenacin)	Enablex® [50] (darifenacin)	Ditropan XL® [35] (oxybutynin)	
Dose (regimen)	**8 mg (once-daily)**	**4 mg (once-daily)**		**20 mg (twice-daily)**	**60 mg (once-daily)**	**10 mg (once-daily)**	**15 mg (once-daily)**	**20 mg (once-daily)**	
Active Moiety	**5-HMT**	**tolterodine**	**5-HMT**	**trospium**	**trospium**	**solifenacin**	**darifenacin**	**oxybutynin**	**desethyl-oxybutynin**
Systemic Bioavailability of Active Moiety	52%	17% (EM) 65% (PM)	NR	9.6%	1.6%*	~90%	19%	NR	NR
Dose Excreted as Active Moiety in Urine	16%	~1%	~14%	60% of urinary excretion	60% of urinary excretion	15%	3%	0.1%	0.1%
Active Moiety Excreted in Urine, mg**	1.3	0.04	0.56	2.3	0.38	1.5	0.45	0.02	0.02

*Based on absolute bioavailability of Sanctura® and the plasma area under the curve of trospium following of Sanctura® XR vs. Sanctura®.
**Computed based on highest dose and % of dose excreted in urine (dose, bioavailability and % of urinary excretion for Sanctura®).
NR=not reported.

4. Clinical Pharmacokinetic Studies of Fesoterodine Versus Tolterodine

From an overall safety, tolerability and efficacy perspective, following administration of therapeutic doses of a drug, it becomes desirable to achieve a narrower and more predictable range of systemic concentrations of the drug and/or its active metabolite(s) across patients. This allows the physician to use the drug in different patient types with a reasonable expectation of the effects in individual patients based on the results of controlled clinical trials.

Findings from studies assessing the pharmacokinetics (PK) of tolterodine and fesoterodine suggest that the PK variability observed after dosing with tolterodine appears to be attributable to the tolterodine molecule rather than 5-HMT. In an open-label, multiple-dose study, the PK of tolterodine extended release (ER) were investigated in healthy volunteers [15]. Because CYP2D6 is the predominant elimination pathway for tolterodine and results in the formation of 5-HMT, both tolterodine and 5-HMT are active. Therefore the sum of both active moieties is relevant to the effects of tolterodine. Fig. (**3**) demonstrates the serum concentration versus time profiles of the 2 active moieties separately and also combined following oral administration of tolterodine ER, with each plot line representing individual subjects in a heterogeneous population of CYP2D6 EMs and PMs. In patients with normal CYP2D6 activity (EMs), roughly equal concentrations of tolterodine and 5-HMT are seen. However, in patients with CYP2D6 activity absent (PMs), the tolterodine concentrations are several-fold higher than those in EMs (Panel A) whilst 5-HMT is not quantifiable (Panel B). As a consequence, when tolterodine was administered to a group of CYP2D6 EMs and PMs, the active moiety concentrations varied over a wide range (almost 2 orders of magnitude) as apparent in Panel C [15].

When we separate the active moiety concentrations into individual contributions from tolterodine and 5-HMT, it is apparent that unchanged tolterodine is the primary source of variability, whereas 5-HMT exposures are maintained within a relatively narrow range (Fig. **3**). For instance, examination of peak exposures indicates that the lowest and highest values are 6-fold apart for tolterodine but only 4-fold apart for 5-HMT. The C_{max} of tolterodine varies between 1-60 nM [15], whereas the C_{max} of 5-HMT only varies between 3-13 nM [55]. This is primarily related to CYP2D6 activity, as PMs have the highest tolterodine concentrations. Since tolterodine and 5-HMT are similar antimuscarinic agents, the less variable pharmacokinetics of 5-HMT makes it a more desirable therapeutic molecule.

Based on these data, it would be ideal to deliver 5-HMT without reliance on tolterodine or CYP2D6, which is precisely what has been accomplished by developing fesoterodine as a prodrug of 5-HMT. Fesoterodine itself is inactive and is converted rapidly and extensively by esterases to form 5-HMT, the singular active moiety in case of fesoterodine. In a separate open-label, single-dose study, the PK and dose proportionality investigation of fesoterodine sustained release (SR) were investigated in healthy volunteers [55]. In this study of fesoterodine in CYP2D6 PMs and EMs, each subject- whether EM or PM- has exposure to 5-HMT because its formation does not depend on CYP2D6. After fesoterodine administration, the inherent lower variability of 5-HMT is maintained as was seen with tolterodine, without the high variability associated with tolterodine.

Although these data were obtained from 2 separate studies in which tolterodine or fesoterodine were administered to a heterogeneous group of EMs and PMs, comparisons of active moieties are of interest and valid, given the objective nature of PK measurements and the inclusion of subjects genotyped as EMs and PMs in both studies [15, 55, 56]. While the fesoterodine study was single-dose, these data are representative of steady state because fesoterodine does not accumulate and the PK are time invariant. The individual

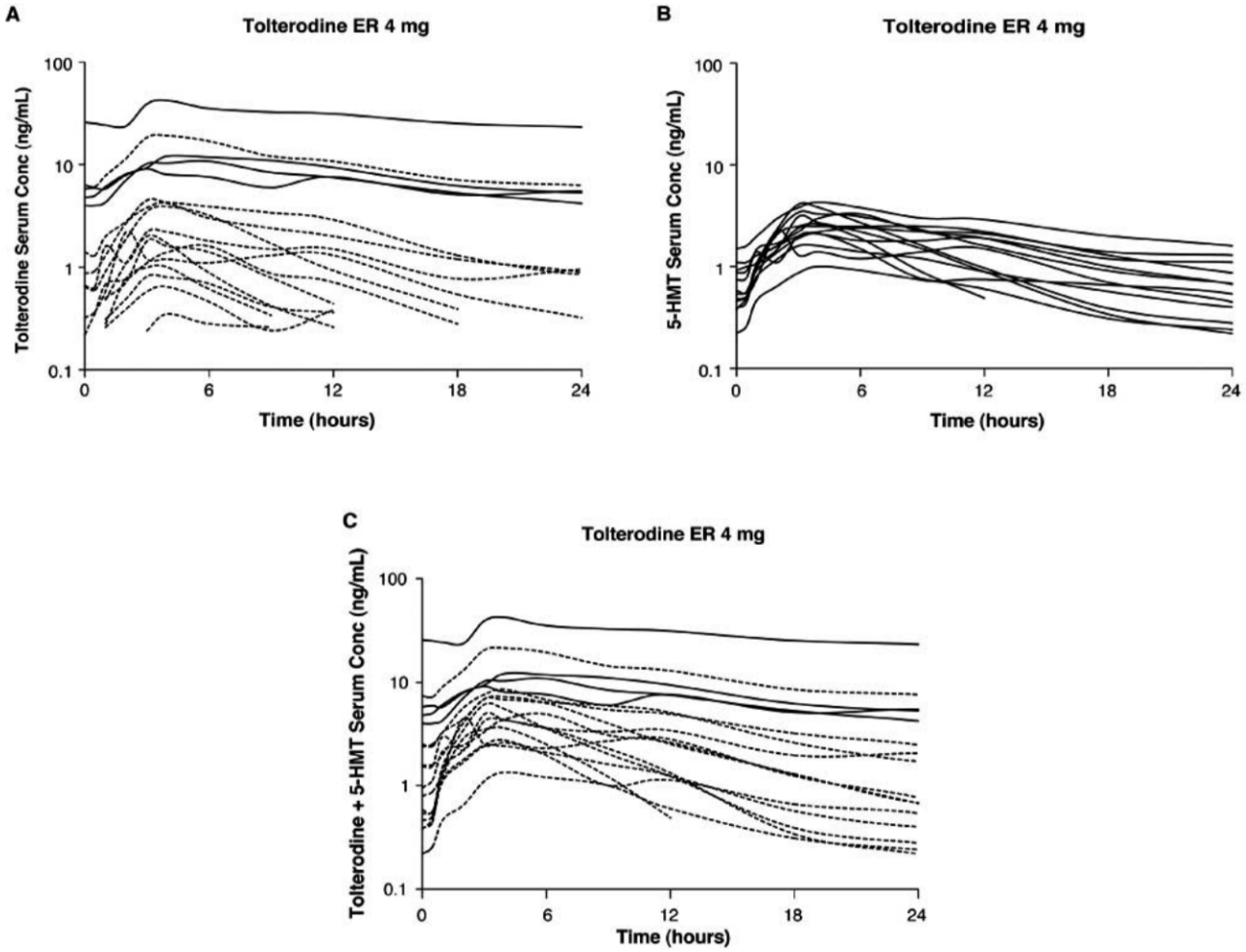


Fig. (3). Serum Concentrations of Active Moieties following Administration of Tolterodine 4 mg: (**A**) Tolterodine; (**B**) 5-HMT; (**C**) Sum of Active Moieties [15]. Solid curves represent CYP2D6 PMs and dashed curves represent CYP2D6 EMs; EMs: Extensive Metabolizers; PMs: Poor Metabolizers.

profiles in the graph for fesoterodine (Fig. **4**) fall within a much narrower range than the profiles for tolterodine ER. This indicates that the range of exposures to active moiety (i.e., PK variability) across subjects is considerably less variable for fesoterodine than it is for tolterodine ER. When the dose of fesoterodine is increased to 8 mg, the resulting exposure range from fesoterodine remains similarly narrow. At higher exposures, efficacy generally reaches a ceiling due to receptor saturation but the incidence of some adverse events may increase. It is because of the lower PK variability that more patients are likely to fall within the therapeutic range after either dose of fesoterodine. Therefore, it may be concluded that fesoterodine delivers markedly reduced variability in total active moieties relative to tolterodine, in part allowing for the development of a higher dose of fesoterodine. Higher drug exposures with fesoterodine 8 mg combined with lower variability may improve consistency and predictability of symptom response, allowing individualization of therapy in patients treated for OAB.

In various Phase 1 studies in healthy volunteers, fesoterodine doses from 4 to 28 mg exhibited dose-proportional increase in 5-HMT exposures, without significant changes in time to maximal concentration or half life across doses [16, 55, 56]. Following fesoterodine administration, both C_{max} and AUC of 5-HMT showed low coefficient of variation, suggesting reproducibility. In two Phase 2 studies, fesoterodine has been administered to OAB patients without significant safety concerns up to the supratherapeutic dose of 12 mg; the efficacy analyses showed that the 12-mg dose of fesoterodine provided no further appreciable incremental benefit compared with the 8-mg dose [57, 58].

5. Clinical Efficacy of Fesoterodine

In a pooled analysis of two phase 3 trials, it was demonstrated that fesoterodine has the ability to significantly reduce OAB symptoms, including urgency and UUI, in a dose-dependent fashion [59]. The 8-mg dose provides significant additional benefit in improving most bladder diary variables compared with the lower dose and allows for dose escalation and individualization in subjects with OAB. This allows subjects to achieve a better balance between treatment efficacy and tolerability. In a Phase 3 trial, fesoterodine 4 mg provided numerically greater symptom relief in nearly all effi-

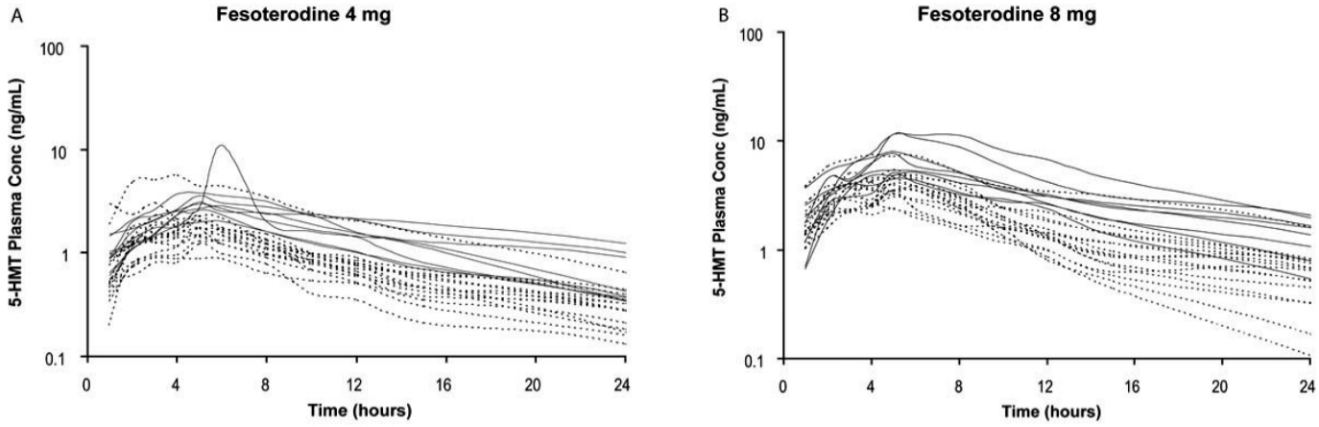


Fig. (4). Plasma Concentrations of The Active Moiety, 5-HMT, following Administration of Fesoterodine 4 and 8 mg: (**A**) 4 mg Dose; (**B**) 8 mg Dose [55]. Solid curves represent CYP2D6 PMs and dashed curves represent CYP2D6 EMs; 5-HMT: 5-hydroxymethyl tolterodine; EMs: Extensive Metabolizers; PMs: Poor Metabolizers

cacy variables than tolterodine 4 mg; fesoterodine 8 mg demonstrated significant and clinically relevant improvement in symptoms over tolterodine ER 4 mg [37].

CONCLUSIONS

While tolterodine and fesoterodine share 5-HMT as a common metabolite, regardless of CYP2D6 genotype, all patients receiving fesoterodine are more consistently exposed only to the less lipophilic active moiety, 5-HMT. Fesoterodine is available at a higher 8 mg daily dose with good tolerability and incremental efficacy.

ACKNOWLEDGEMENTS

This study was funded by Schwarz BioSciences GmbH and Pfizer Inc. Editorial assistance was provided by Nancy Sheridan from Complete Healthcare Communications, Inc. and was funded by Pfizer Inc.

REFERENCES

[1] Abrams, P. Reviewing the ICS 2002 Terminology Report: The Ongoing Debate. *Neurourol. Urodyn.* **2006**, *25*, 293-94.

[2] Andersson, K. E. Treatment-resistant detrusor overactivity--underlying pharmacology and potential mechanisms. *Int. J. Clin. Pract. Suppl.* **2006**, (151), 8-16.

[3] Andersson, K.-E. Antimuscarinics for the treatment of overactive bladder. *Lancet Neurol.* **2004**, *3* (1), 46-53.

[4] Finney, S. M.; Andersson, K. E.; Gillespie, J. I.; Stewart, L. H. Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? *BJU Int.* **2006**, *98* (3), 503-7.

[5] Andersson, K. E. Current concepts in the treatment of disorders of micturition. *Drugs.* **1988**, *35* (4), 477-94.

[6] Chapple, C. R. Muscarinic receptor antagonists in the treatment of overactive bladder. *Urology.* **2000**, *55* (5A Suppl), 33-46.

[7] Kelleher, C. J.; Cardozo, L. D.; Khullar, V.; Salvatore, S. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br. J. Obstet. Gynaecol.* **1997**, *104* (9), 988-93.

[8] Nilvebrant, L.; Hallen, B.; Larsson, G. Tolterodine–a new bladder selective muscarinic receptor antagonist: preclinical pharmacological and clinical data. *Life Sci.* **1997**, *60*, 1129-36.

[9] Detrol® (tolterodine tartrate tablets). Full Prescribing Information, Pharmacia & Upjohn Company, Kalamazoo, MI, **2003**.

[10] Detrol LA® (tolterodine tartrate). Full Prescribing Information, Pharmacia & Upjohn Company, Kalamazoo, MI, **2005**.

[11] Nilvebrant, L.; Pahlman, I.; d'Argy, R. In *Tissue distribution of tolterodine and its metabolites: low penetration into the central nervous system*, Meeting of the European Association of Urology, Brussels, Belgium, April 12-15; Brussels, Belgium, **2000**.

[12] Salvatore, S.; Serati, M.; Digesu, G. A.; Triacca, P.; Uccella, S.; Khullar, V.; Bolis, P. Efficacy of tolterodine in relation to different urodynamic findings of detrusor overactivity. *Int. Urogynecol. J. Pelvic Floor Dysfunct.* **2008**, *19* (5), 701-4.

[13] van Kerrebroeck, P. Clinical study results of tolterodine in patients with overactive bladder. *Expert Rev. Neurotherap.* **2003**, *3*, 155-63.

[14] Nilvebrant, L. The mechanism of action of tolterodine. *Rev Contemp Pharmacother.* **2000**, *11*, 13-27.

[15] Olsson, B.; Szamosi, J. Multiple dose pharmacokinetics of a new once daily extended release tolterodine formulation versus immediate release tolterodine. *Clin. Pharmacokinet.* **2001**, *40* (3), 227-35.

[16] Cawello, W.; Auer, S.; Hammes, W.; Sachse, R.; Horstmann, R. Multiple dose pharmacokinetics of fesoterodine in human subjects [abstract]. *Naunyn. Schmiedebergs Arch. Pharmacol.* **2002**, *365* (suppl 1), 428.

[17] Michel, M. C. Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. *Expert Opin. Pharmacother.* **2008**, *9* (10), 1787-96.

[18] Ney, P.; Breidenbach, A.; Pandita, R. K.; Stoehr, T.; Andersson, K. E. Pharmacological characterization of a novel investigational antimuscarinic drug, fesoterodine, *in vitro* and *in vivo*. *BJU Int.* **2008**, *101* (8), 1036-42.

[19] Gillberg, P. G.; Sundquist, S.; Nilvebrant, L. Comparison of the *in vitro* and *in vivo* profiles of tolterodine with those of subtype-selective muscarinic receptor antagonists. *Eur. J. Pharmacol.* **1998**, *349* (2-3), 285-92.

[20] Nilvebrant, L.; Andersson, K. E.; Gillberg, P. G.; Stahl, M.; Sparf, B. Tolterodine–a new bladder-selective antimuscarinic agent. *Eur. J. Pharmacol.* **1997**, *327* (2-3), 195-207.

[21] Nilvebrant, L.; Gillberg, P. G.; Sparf, B. Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. *Pharmacol. Toxicol.* **1997**, *81* (4), 169-72.

[22] *European Medicines Agency (EMEA): EPARs for authorized medicinal products for human use. European Public Assessment Report for Toviaz (Scientific Discussion)*; **2007**.

[23] Mansfield, K. J.; Liu, L.; Mitchelson, F. J.; Moore, K. H.; Millard, R. J.; Burcher, E. Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: changes in ageing. *Br. J. Pharmacol.* **2005**, *144* (8), 1089-99.

[24] Ohtake, A.; Ukai, M.; Hatanaka, T.; Kobayashi, S.; Ikeda, K.; Sato, S.; Miyata, K.; Sasamata, M. *In vitro* and *in vivo* tissue selectivity

profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats. *Eur. J. Pharmacol.* **2004**, *492* (2-3), 243-50.
[25] Abrams, P.; Andersson, K. E. Muscarinic receptor antagonists for overactive bladder. *BJU Int.* **2007**, *100* (5), 987-1006.
[26] Nasal, A.; Siluk, D.; Kaliszan, R. Chromatographic retention parameters in medicinal chemistry and molecular pharmacology. *Curr. Med. Chem.* **2003**, *10* (5), 381-426.
[27] Pascual, J.; Munoz, P. Correlation between lipophilicity and triptan outcomes. *Headache.* **2005**, *45* (1), 3-6.
[28] Doroshyenko, O.; Jetter, A.; Odenthal, K. P.; Fuhr, U. Clinical pharmacokinetics of trospium chloride. *Clin. Pharmacokinet.* **2005**, *44* (7), 701-20.
[29] Maniscalco, M.; Singh-Franco, D.; Wolowich, W. R.; Torres-Colon, R. Solifenacin succinate for the treatment of symptoms of overactive bladder. *Clin. Ther.* **2006**, *28* (9), 1247-72.
[30] Chapple, C. R. Darifenacin: a novel M3 muscarinic selective receptor antagonist for the treatment of overactive bladder. *Expert Opin Investig Drugs* **2004**, *13* (11), 1493-500.
[31] Malhotra, B.; Wood, N.; R., S.; Gandelman, K. In *Lipophilicity of 5-Hydroxymethyl Tolterodine, the Active Metabolite of Fesoterodine*, British Pharmacological Society Winter Meeting, Brighton, UK, Brighton, UK, **2008**.
[32] Goodman Gilman, A.; Rall, T. W.; Nies, A. S.; Taylor, P. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 8th ed.; McGraw-Hill Medical Publishing Division: New York, NY, **1990**.
[33] Kay, G. G.; Abou-Donia, M. B.; Messer, W. S., Jr.; Murphy, D. G.; Tsao, J. W.; Ouslander, J. G. Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *J. Am. Geriatr. Soc.* **2005**, *53* (12), 2195-201.
[34] Todorova, A.; Vonderheid-Guth, B.; Dimpfel, W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J. Clin. Pharmacol.* **2001**, *41* (6), 636-44.
[35] Ditropan® XL (oxybutynin chloride). Full Prescribing Information, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2004.
[36] Toviaz® (fesoterodine fumarate). Full Prescribing Information, Pfizer Inc, New York, NY, **2007**.
[37] Chapple, C. R.; Van Kerrebroeck, P. E.; Junemann, K. P.; Wang, J. T.; Brodsky, M. Comparison of fesoterodine and tolterodine in patients with overactive bladder. *BJU Int.* **2008**, *102*, 1128-32.
[38] van Kerrebroeck, P.; Kreder, K.; Jonas, U.; Zinner, N.; Wein, A. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology.* **2001**, *57* (3), 414-21.
[39] Beers, R.; Camporesi, E. Remifentanil update: clinical science and utility. *CNS Drugs* **2004**, *18* (15), 1085-104.
[40] Charasson, V.; Bellott, R.; Meynard, D.; Longy, M.; Gorry, P.; Robert, J. Pharmacogenetics of human carboxylesterase 2, an enzyme involved in the activation of irinotecan into SN-38. *Clin. Pharmacol. Ther.* **2004**, *76* (6), 528-35.
[41] Imai, T. Human carboxylesterase isozymes: catalytic properties and rational drug design. *Drug Metab. Pharmacokinet.* **2006**, *21* (3), 173-85.
[42] Fesoterodine: European Patent Specification. **2002**.
[43] Brynne, N.; Dalen, P.; Alvan, G.; Bertilsson, L.; Gabrielsson, J. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamic of tolterodine. *Clin. Pharmacol. Ther.* **1998**, *63* (5), 529-39.
[44] Xie, H. G.; Kim, R. B.; Wood, A. J.; Stein, C. M. Molecular basis of ethnic differences in drug disposition and response. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 815-50.
[45] Brynne, N.; Forslund, C.; Hallen, B.; Gustafsson, L. L.; Bertilsson, L. Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity. *Br. J. Clin. Pharmacol.* **1999**, *48* (4), 564-72.
[46] Olsson, B.; Landgren, B. M. The effect of tolterodine on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive containing ethinyl estradiol and levonorgestrel. *Clin. Ther.* **2001**, *23* (11), 1876-88.
[47] Malhotra, B.; Sachse, R.; Wood, N. Evaluation of drug-drug interactions with fesoterodine. *Eur. J. Clin. Pharmacol.* **2009**, *65*, 551-60.
[48] Sachse, R.; Cawello, W.; Horstmann, R. In *Safety, tolerability and pharmacokinetics of fesoterodine after co-treatment with the potent cytochrome P450 3A4 inhibitor ketoconazole*, International Continence Society Annual Meeting, Paris, France, August 25-27; Paris, France, **2004**.
[49] Brynne, N.; Svanstrom, C.; Aberg-Wistedt, A.; Hallen, B.; Bertilsson, L. Fluoxetine inhibits the metabolism of tolterodine-pharmacokinetic implications and proposed clinical relevance. *Br. J. Clin. Pharmacol.* **1999**, *48* (4), 553-63.
[50] Enablex® (darifenacin hydrobromide). Full Prescribing Information, Novartis Pharma Stein AG, Stein, Switzerland, **2005**.
[51] Sanctura® (trospium chloride). Full Prescribing Information, Allergan, Inc., Irvine, CA, **2007**.
[52] Sanctura XR (trospium chloride). Full Prescribing Information, Allergan, Inc, Irvine, CA, **2007**.
[53] VESIcare® (solifenacin succinate). Full Prescribing Information, Astella Pharma Technologies, Inc., Norman, OK, and GlaxoSmithKline, Research Triangle Park, NC, **2007**.
[54] Kim, Y.; Yoshimura, N.; Masuda, H.; de Miguel, F.; Chancellor, M. B. Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways. *Urology* **2005**, *65* (2), 238-42.
[55] Malhotra, B. K.; Guan, Z.; Wood, N.; Gandelman, K. Pharmacokinetic profile of fesoterodine. *Int. J. Clin. Pharmacol. Ther.* **2008**, *46* (11), 556-63.
[56] Simon, H. U.; Malhotra, B. The pharmacokinetic profile of fesoterodine: similarities and differences to tolterodine. *Swiss Med. Wkly.* **2009**, *139*(9-10), 146-51.
[57] Chapple, C. Fesoterodine, a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome: results of a phase 2 controlled study. *Neurourol. Urodyn.* **2004**, *23* (5-6), 598-99.
[58] Nitti, V.; Wiatrak, M.; Kreitman, L.; Lipsitz, D. Fesoterodine is an effective antimuscarinic for patients with overactive bladder (OAB): results of a phase 2 trial. Available at: http://www.icsoffice.org/publications/2005/PDF/0306.pdf.
[59] Khullar, V.; Rovner, E. S.; Dmochowski, R.; Nitti, V.; Wang, J.; Guan, Z. Fesoterodine dose response in subjects with overactive bladder syndrome. *Urology* **2008**, *71* (5), 839-43.

Received: June 12, 2009 **Revised: September 23, 2009** **Accepted: September 26, 2009**