Expert Opinion

Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome

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Background: Fesoterodine is a newly approved drug for the treatment of overactive bladder syndrome. *Objective*: The aim of this study was to review the preclinical and clinical data on fesoterodine. *Methods*: The study involved a search of the Medline database and the proceedings volumes of urological congresses. *Results/conclusions*: Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine by non-specific esterases. 5-Hydroxymethyltolterodine is a muscarinic receptor antagonist. Fesoterodine is primarily eliminated as inactive metabolites along with significant renal excretion as the unchanged active metabolite 5-hydroxymethyltolterodine. Fesoterodine is indicated for use at doses of 4 and 8 mg once daily. In clinical studies both doses of fesoterodine were consistently superior to placebo in improving the symptoms of overactive bladder syndrome, with 8 mg/day having significantly greater effects than 4 mg/day.

Keywords: blood–brain barrier, cytochrome P450 2D6, fesoterodine, 5-hydroxymethyltolterodine, muscarinic receptor antagonist, overactive bladder syndrome

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1. Overview of the market

Overactive bladder syndrome (OAB) is present in ~ 16% of the adult population and muscarinic receptor antagonists are the standard of care in its treatment [1]. More recently they have also been considered for the treatment of male lower urinary tract symptoms, which historically have been attributed to benign prostatic hyperplasia [2]. Several representatives of this class are available, including darifenacin, oxybutynin, propiverine, solifenacin, tolterodine and trospium, with tolterodine being the global market leader. While generally well tolerated, their efficacy relative to placebo is only moderate [1,3]. While several of these drugs have multiple registered doses, dose dependency is only poorly established. Moreover, many of these drugs have usage restrictions in special patient populations. Other drug classes have not been approved for use in OAB, but botulinum toxin and β_3-adrenoceptor agonists are currently in advanced clinical development.

2. Introduction to the compound

Fesoterodine functions as an orally active prodrug that is converted to its active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases. 5-Hydroxymethyltolterodine is a competitive muscarinic receptor antagonist.

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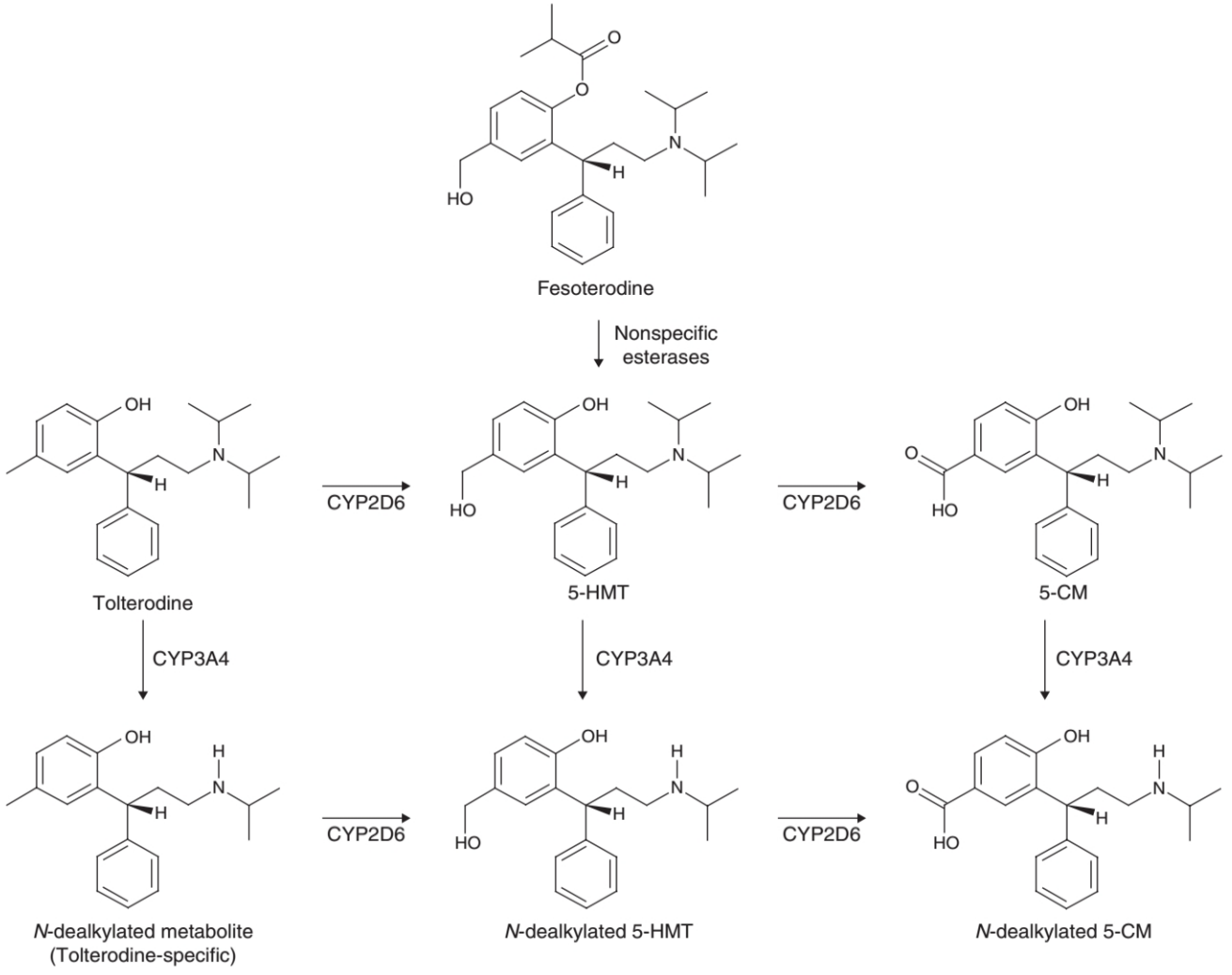

Figure 1. Schematic depiction of the metabolism of tolterodine and fesoterodine.
Courtesy of Pfizer Inc.
5-CM: 5-Carboxy metabolite of 5-HMT.

3. Chemistry

The structures of fesoterodine and 5-HMT are shown in **Figure 1**. 5-Hydroxymethyltolterodine is chemically identical to an active metabolite of tolterodine, which has also been mentioned in previous reports under the code names DD01, PNU-200577 or SPM 7605.

4. Pharmacodynamics

Following oral administration fesoterodine is rapidly and completely metabolised to 5-HMT and the parent compound fesoterodine is not detected in the peripheral blood (see below). Therefore, most of the preclinical and clinical pharmacology of fesoterodine is relevant and discussed in relation to the active metabolite 5-HMT rather than the parent compound fesoterodine.

The pharmacological properties of 5-HMT have been investigated in radioligand binding studies with cloned human muscarinic receptor subtypes and with endogenously expressed receptors in the urinary bladder, salivary glands and other tissues. An early study reported 5-HMT affinities (K_i values) of 2.3, 2.0, 2.5, 2.8 and 2.9 nM at cloned M_1, M_2, M_3, M_4 and M_5 receptors, respectively, whereas tolterodine exhibited slightly but consistently lower affinities of 3.0, 3.8, 3.4, 5.0 and 3.4 nM, respectively [4]. A later study largely confirmed these findings and additionally reported that the parent drug fesoterodine had much lower affinities at all muscarinic receptor subtypes (631, 501, > 1000, 158 and > 1000 nM, respectively) [5]. The affinities of 5-HMT, as determined in studies in the urinary bladder, salivary glands and other tissues of guinea-pigs [4], mice [6,7] and humans [8], are consistent with the data from the cloned human receptor subtypes (**Table 1**). Thus,

Table 1. Affinities of tolterodine, fesoterodine and 5-HMT in radioligand binding studies and functional experiments.

	Tolterodine	Fesoterodine	5-HMT	Ref.
Binding to cloned human muscarinic receptors (-log K_i)				
M_2	8.4	ND	8.7	[4]
M_2	8.2	6.3	8.8	[5]
M_3	8.5	ND	8.6	[4]
M_3	7.9	< 6.0	8.2	[5]
Binding to muscarinic receptors in tissues (-log K_i)				
Guinea pig bladder	8.6	ND	8.5	[4]
Mouse bladder	8.9	ND	9.1	[6]
Mouse bladder	8.9	ND	9.1	[7]
Human bladder (detrusor)	ND	8.6	ND	[8]
Human bladder (urothelium)	ND	8.6	ND	[8]
Guinea pig salivary gland	8.3	ND	8.3	[4]
Mouse salivary gland	8.9	ND	8.9	[6]
Guinea pig heart	8.8	ND	9.0	[4]
Mouse heart	8.7	ND	9.1	[6]
Functional in vitro antagonism in the bladder (pK_B)				
Rat	ND	8.7	8.8	[5]
Guinea pig	8.5	ND	9.1	[11]
Human	9.0	ND	9.0	[12]

ND: Not determined.

based on pharmacological characterisation combined with undetectable systemic exposure of fesoterodine after its oral administration to humans, the parent drug fesoterodine at its therapeutic doses is considered pharmacologically inactive and its clinical effects appear to be fully mediated by 5-HMT [9]. Furthermore, 5-HMT lacks relevant affinity for a range of more than 50 other molecular targets [10]. These data demonstrate that 5-HMT, as the active metabolite of fesoterodine, has a high selectivity for muscarinic receptors and recognises all of their subtypes with similar affinity. Nevertheless, a slightly higher affinity for muscarinic receptors in the bladder as compared to those in the salivary glands has been reported consistently across several studies (**Table 1**): this tissue selectivity can most likely be explained by differential tissue penetration [6].

Functional *in vitro* studies on the effects of 5-HMT have been reported from isolated bladder strips of rats [5], guinea-pigs [11] and humans [12]. 5-Hydroxymethyltolterodine caused a concentration-dependent parallel right shift of the concentration–response curve of the muscarinic receptor agonist carbachol in rats without affecting the maximal carbachol response: based upon this competitive antagonism an affinity (K_B value) of 1.6 nM was calculated [5], which is in good agreement with the radioligand binding data. A similar apparent potency of fesoterodine under the same experimental conditions indicated rapid conversion of fesoterodine to 5-HMT by the bladder strips. 5-Hydroxymethyltolterodine also inhibited contraction of the rat bladder upon electrical field stimulation, that is due to the release of endogenous agonist, in a concentration-dependent manner and a concentration of 0.1 µM was sufficient for maximal inhibition [5]. Competitive antagonism with a similarly high potency was demonstrated for 5-HMT in bladder strips from guinea-pigs [4] and humans (**Table 1**) [12]. In the latter study 5-HMT also inhibited the contraction induced by field stimulation but not the receptor-independent contraction evoked by KCl, confirming the specificity of this drug for muscarinic receptors.

In cystometric *in vivo* studies in female rats intravenous 5-HMT at a dose of 0.01 mg/kg significantly increased bladder capacity by 10% and contraction intervals by 11% and reduced micturition pressure by 63% [5]: similar findings were also obtained with intravenous administration of fesoterodine. In similar studies with anaesthetised cats 5-HMT inhibited bladder contraction with an ID_{50} of 15 nmol/kg, whereas a 50% inhibition of salivary secretion required a dose of 40 nmol/kg ($p < 0.05$ versus the bladder), while in parallel experiments the potency of tolterodine

was consistently lower for both effects (ID_{50} values 101 and 257 nmol/kg, respectively) [4,11].

Oral fesoterodine or 5-HMT at doses of 30 mg/kg did not increase the gastrointestinal transit time in mice, whereas atropine (20 mg/kg), darifenacin (10 and 30 mg/kg) and solifenacin (10 and 30 mg/kg) inhibited the transit time by 33, 18 – 25 and 20 – 29%, respectively [13].

Dedicated clinical studies on the possible adverse effects of 5-HMT on the CNS have not been reported yet. However, the CNS penetration of a drug depends largely on its lipophilicity [14]. In this regard 5-HMT has a much lower lipophilicity than tolterodine (the octanol:water coefficient expressed as log *D* values was 0.74 versus 1.83) or other clinically used muscarinic receptor antagonists except for trospium [15,16]. Following oral administration of radiolabelled tolterodine only a small fraction of the radioactivity reaches the CNS and a CNS:blood ratio of radioactivity of 0.1 – 0.3 was reported in mice [15]. Consistent with the lower lipophilicity of 5-HMT relative to tolterodine, the CNS penetration of 5-HMT (assessed following oral administration of radiolabelled fesoterodine) was even lower and a CNS:blood ratio of only 0.04 – 0.07 was reported in mice [16]. These data indicate that, due to its low lipophilicity, 5-HMT exhibits a very low CNS penetration. This is consistent with data from mice, where > 80% of circulating active drug following tolterodine dosing was 5-HMT and even considerably supratherapeutic doses did not affect memory [17]. Whether this translates into a clinically relevant advantage cannot be decided definitively based upon the presently available data, as tolterodine in doses up to 0.3 mg/kg also did not affect memory formation in rats under conditions where the same dose of oxybutynin or scopolamine significantly impaired it [18]. In non-selected groups of patients, including specific studies in the elderly [19], CNS-related adverse effects have typically not been reported with the use of tolterodine, but case reports have indicated that tolterodine may induce memory impairment or hallucinations in some individuals [20-23]. A recently reported dedicated study in volunteers detected no adverse effects of tolterodine on cognitive function [24]. However, in a subgroup analysis of this study the phenotype for drug metabolism by CYP2D6 [25] appeared to play a relevant role in adverse effects on rapid eye movement (REM) sleep. Thus, volunteers with the more frequently expressed 'extensive metaboliser' (EM) phenotype, who can effectively convert tolterodine to 5-HMT, exhibited no impairment of their REM sleep. In contrast, volunteers with the 'intermediate metaboliser' (IM) or 'poor metaboliser' (PM) phenotype, who produce little 5-HMT from tolterodine [26], showed impaired REM sleep upon tolterodine treatment, that is the relative contribution of REM sleep declined significantly from 21.8 to 17.4% [24]. These data indicate that the risk of CNS adverse events could be even lower with fesoterodine than with tolterodine, particularly in patients with the IM or PM phenotype with regard to CYP2D6: however, this remains to be confirmed in dedicated clinical studies.

Taken together, the available preclinical pharmacology data demonstrate that 5-HMT is a high-affinity, competitive antagonist of muscarinic receptors in the urinary bladder of several species, including humans and its potency is in good agreement with data from radioligand binding studies. Starting at low doses 5-HMT affects bladder function *in vivo* in experimental animals, as is to be expected from a muscarinic receptor antagonist. In direct comparative studies 5-HMT has an antagonist potency that is similar to or slightly higher than tolterodine. Consistent with its physicochemical difference to tolterodine, that is hydroxylation, 5-HMT exhibits less CNS penetration and, in patients with the IM or PM phenotype, this could translate into an even lower risk of CNS adverse events with fesoterodine.

5. Pharmacokinetics and metabolism

Following oral administration fesoterodine is not detected in the peripheral blood, thereby indicating a rapid and complete conversion to 5-HMT by non-specific esterases [9]. Although 5-HMT is also a metabolite of tolterodine, there is an important distinction: unlike fesoterodine, tolterodine metabolism to 5-HMT is mediated by CYP2D6 (**Figure 1**) and is subject to the CYP2D6 phenotype of the patient. Accordingly, subjects with the EM phenotype of CYP2D6 exhibit roughly similar serum concentrations of tolterodine and 5-HMT [11,27]. However, in subjects with the PM phenotype their plasma concentrations of tolterodine are considerably higher, with low or even undetectable levels of 5-HMT [27]. Accordingly, the mean C_{max} value and AUC of tolterodine can be five and 10 times higher, respectively, in subjects with the PM phenotype as compared to the EM phenotype with regard to CYP2D6 [28]. Individual C_{max} and AUC values span a range of over 100-fold across the genotypes [28]. In contrast, average plasma concentrations of 5-HMT following oral administration of fesoterodine differ by less than a factor of 2 in subjects with the PM and EM phenotypes, for example the values are 1.89 versus 3.45 ng/ml, respectively, following a single dose of 4 mg of fesoterodine [29].

A significant proportion of 5-HMT is excreted renally without additional metabolism and the renal clearance of 5-HMT is ~ 250 ml/min, with > 15% of the administered fesoterodine dose excreted as unchanged 5-HMT [30]. This raises the possibility that 5-HMT also could work from the luminal side of the bladder, an effect that may be clinically relevant based upon current discussions around the role of muscarinic receptors in the urothelium [31,32].

In addition to renal excretion, multiple pathways exist for the metabolism of 5-HMT to inactive metabolites. In this regard CYP2D6 and CYP3A4 are the two alternative and equally prominent pathways that form its carboxy and *N*-desisopropyl metabolites, respectively:

each in turn is further metabolised to the final carboxy-*N*-desisopropyl metabolite [11]. Each of these three secondary metabolites is pharmacologically inactive. In addition to 5-HMT, the inactive metabolites are also common between fesoterodine and tolterodine. The metabolic pathways of tolterodine and fesoterodine are shown schematically in **Figure 1** (the enzymes involved in the formation of the secondary metabolites have not been experimentally confirmed in all cases).

The prodrug fesoterodine is absorbed almost completely from the gut, but non-specific esterases metabolise it rapidly and completely so that only 5-HMT is detectable in the peripheral blood after oral administration of fesoterodine [9]. This is also consistent with undetectable fesoterodine not only in the blood but also an absence of any appreciable fesoterodine being excreted in the urine or faeces. Although fesoterodine is completely converted to form 5-HMT, some of the converted 5-HMT is metabolised presystemically: nevertheless, the absolute bioavailability of 5-HMT from orally administered fesoterodine remains high, averaging ~ 52% [33]. The pharmacokinetics of 5-HMT were found to be dose linear with the administered fesoterodine dose [29]. The appearance of 5-HMT in the blood is food independent [34], which allows fesoterodine to be taken with or without a meal. Specific Phase I studies have not demonstrated any evidence for clinically relevant pharmacokinetic differences between the genders or age groups [35] or between ethnic groups [36].

Fesoterodine has been developed using a sustained release formulation for which the maximal plasma concentrations of 5-HMT are reached after ~ 5 h with a terminal half-life of ~ 7 – 9 h across multiple studies in different populations with single and repeated dosing [9,29,30,34-39]. In line with the half-life, no evidence of accumulation was seen upon fesoterodine treatment for multiple days in those studies. Taken together these pharmacokinetic data support once-daily administration of fesoterodine.

With regard to special patient populations apart from gender, age [35] and ethnicity [36] the standard studies have been performed in patients with impaired kidney or liver function. In this regard one study compared subjects with normal renal function (glomerular filtration rate (GFR) > 80 ml/min) and those with a GFR of 50 – 80, 30 – 50 and < 30 ml/min [39]. Following log-transformation the 5-HMT peak plasma concentrations in the renal impairment groups relative to those in healthy subjects were 1.35, 1.48 and 2.03-fold, respectively: similar findings were obtained for the AUC values. These findings suggest that the starting dose of 4 mg/day of fesoterodine can also be used in patients with impaired renal function and can be titrated, with caution, to 8 mg/day in subjects with mild-to-moderate renal impairment. In contrast, the package inserts of tolterodine and tolterodine extended release (ER) require dose adjustment, at least for patients with severe renal impairment (GFR < 30 ml/min).

In another study the pharmacokinetics of fesoterodine were compared between healthy subjects and patients with moderate impairment of liver function (Child–Pugh B) [38]. In the liver-impaired patients the C_{max} and AUC values were approximately twice the values of the healthy controls, whereas the terminal half-life was not significantly affected. These data indicate that the starting dose of 4 mg/day can also be used in patients with mild-to-moderate hepatic impairment and can be titrated, with caution, to 8 mg/day in subjects with mild hepatic impairment. No data are currently available for patients with severe impairments of liver function and, thus, fesoterodine use is not recommended in these patients. In contrast, the package inserts for tolterodine and tolterodine ER require dose adjustment in all patients with impaired liver function.

Finally, an interaction study with the potent CYP3A4 inhibitor ketoconazol (200 mg) was performed, in which subjects with the EM and PM phenotypes with regard to CYP2D6 were analysed separately [37]. The maximal plasma concentrations of 5-HMT during ketoconazol administration in the EM and PM phenotype subjects were 2.2 and 1.5 times as high as in the absence of ketoconazol, respectively: the AUC value was affected similarly. These data suggest that the standard fesoterodine dose of 4 mg/day can also be used in patients concomitantly receiving potent CYP3A4 inhibitors, regardless of their CYP2D6 phenotype. In contrast, the package inserts for tolterodine and tolterodine ER do not recommend their use upon concomitant treatment with potent CYP3A4 inhibitors.

Formulations allowing once-daily dosing are available for most of the muscarinic receptor antagonists used clinically for OAB treatment. In some cases this is achieved by specific formulations (e.g. oxybutynin, propiverine and tolterodine), while in other cases this is due to the intrinsic pharmacokinetic properties of the drug (darifenacin and solifenacin) [40]. In this regard the very long elimination half-life of ~ 60 h for solifenacin deserves consideration, as it may theoretically lead to accumulation [41].

While some muscarinic receptor antagonists are primarily excreted via the kidneys (e.g. trospium), others are intensively metabolised by the liver (e.g. darifenacin, oxybutynin, propiverine, solifenacin and tolterodine) [42]. Based upon these excretion pathways, dose adjustments are required in patients with impaired kidney or liver function as described in the respective package inserts. In contrast, the standard starting fesoterodine dose can be used in patients with impaired renal or hepatic function due to the combination of renal excretion and hepatic metabolism of 5-HMT.

It is an intriguing observation from the available pharmacokinetic studies with fesoterodine administration that the interindividual variability in drug exposure is relatively small as compared to that reported, for example, for tolterodine (**Figure 2**). Obviously, such comparisons involve various processes, such as absorption, which is highly variable with trospium, metabolism and excretion [40]. In

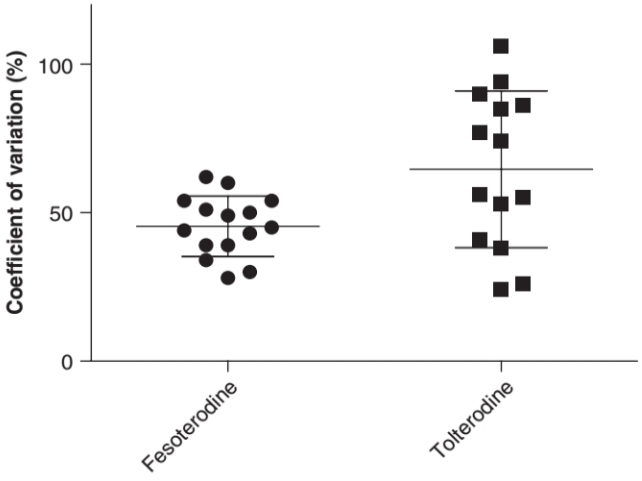

Figure 2. Variability (expressed as coefficients of variation) in maximal plasma concentrations upon oral treatment with fesoterodine (assessed as 5-HMT) in comparison with published data on tolterodine. The figure is based upon published data [9,26,27,29,34-36,38-40,55]. Note that data from both genders and different age and ethnic groups were included, whereas data from diseased subjects (other than OAB) were excluded.

the case of fesoterodine the CYP2D6-independent generation of the active drug moiety appears to be a key explanation for the relatively small variability in 5-HMT exposure. Irrespective of such mechanistic considerations, a relatively small variability in exposure may be therapeutically beneficial, as it may lead to a greater predictability in clinical response. However, whether this indeed translates into a clinically relevant benefit cannot be determined from the presently available data.

6. Clinical efficacy

The clinical efficacy and tolerability of fesoterodine has been explored in 20 Phase I (partly described above), three Phase II and two Phase III studies. This includes a thorough study on the possible effects on QT intervals (see the section on clinical tolerability). Fesoterodine doses of 2, 4, 8 and 12 mg/day were tested in placebo-controlled, randomised, double-blind multicentre trials during the Phase II studies [43,44]. One of these studies also involved urodynamic pressure–flow investigations [45]. The primary efficacy parameter of the Phase II studies was the number of daily micturition and urgency incontinence episodes. In the study performed in the US, which involved an 8-week treatment of only 38 – 47 patients per group, significant improvements relative to placebo were observed for both efficacy parameters, despite the small numbers of subjects, at fesoterodine doses of 4, 8 and 12 mg/day [44]. The second trial, performed in Europe, Israel and South-Africa, involved the same doses but lasted 12 weeks and involved 173 – 186 patients per group [43], that is it had a design and size similar to many previous Phase III studies in this indication. This study also demonstrated significant improvements of both primary efficacy variables relative to placebo. Based on these data on efficacy and tolerability, fesoterodine doses of 4 and 8 mg/day were selected for the pivotal Phase III studies. As the OAB definition by the International Continence Society does not require urodynamic proof of detrusor overactivity [46], one of the Phase II studies had also involved pressure–flow investigations [45]. Their analysis showed similar clinical improvements in patients with and without detrusor overactivity at each fesoterodine dose tested.

The design of the two Phase III studies was in line with the regulatory recommendations by the EMEA and FDA, that is these were placebo-controlled, randomised, double-blind multicentre studies of 12 weeks duration with > 250 patients per treatment group. The inclusion and exclusion criteria were similar to those of studies with other muscarinic receptor antagonists that have been submitted for registration in recent years. One of the two studies (performed in the US) had three arms and compared fesoterodine doses of 4 and 8 mg/day with placebo [47]. The other study (largely performed in Europe) had a very similar design but additionally included a fourth group of patients who received 4 mg/day of tolterodine ER as active control [48]. Secondary analyses of the pooled data from both Phase III studies have also been reported [49,50].

The patients in both Phase III studies had rather similar baseline characteristics and also exhibited rather similar symptom improvements upon treatment [47,48]. Therefore, they are described together. Both doses of fesoterodine were significantly more effective than placebo for the three co-primary efficacy variables of urinary frequency, urgency incontinence episodes and the percentage of patients reporting a treatment response (**Figure 3**), as well as for many secondary efficacy variables including the number of urgency episodes. The extent of symptom improvement was in a range similar to that reported with other muscarinic receptor antagonists in studies of a similar design [1]. Only the symptom of nocturia was not consistently improved by fesoterodine. This is not surprising based upon the low baseline level of nocturia in these studies, the multifactorial causes of nocturia and the observations that other muscarinic receptor antagonists also did not yield consistent nocturia improvements in OAB patients [51]. An efficacy parameter, which has rarely been used in other studies but which may have direct relevance for patients, was the extrapolated number of incontinence-free days per week: this was consistently improved by both fesoterodine doses in both studies.

Although several doses are available for most muscarinic receptor antagonists for OAB treatment, a significantly greater benefit with higher doses has typically not been reported [1]. In contrast, the fesoterodine dose of 8 mg/day

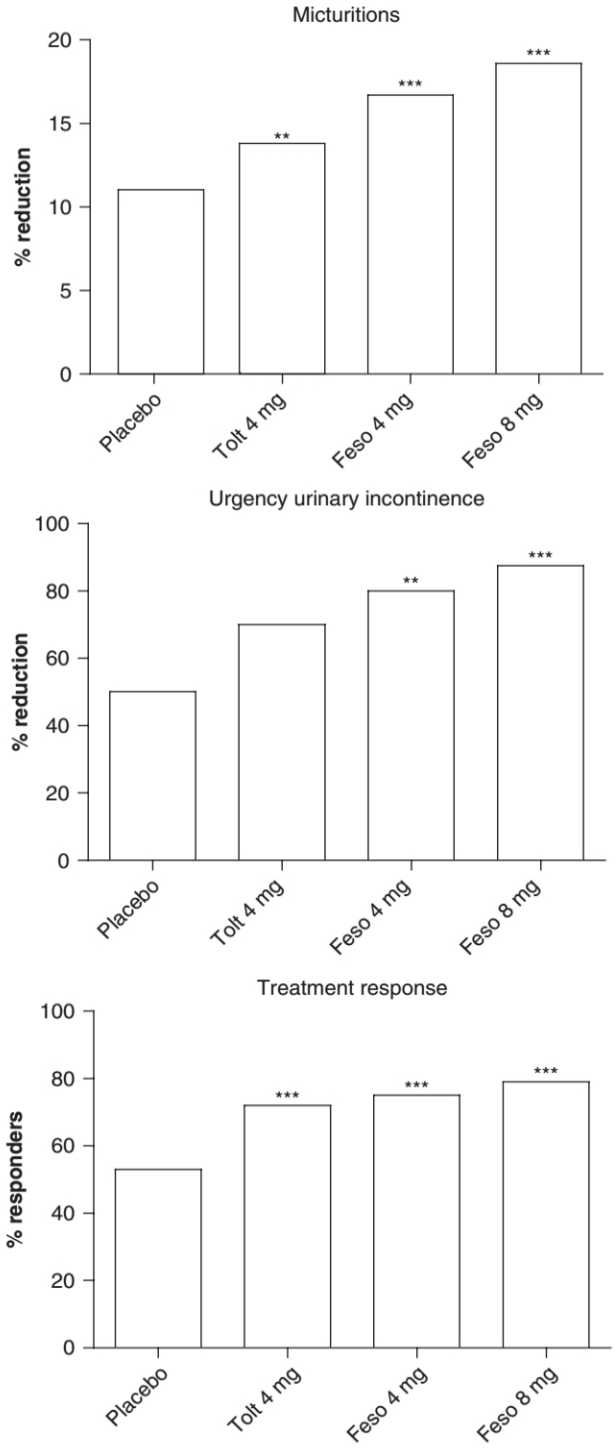

Figure 3. Efficacy of 4 and 8 mg/day of fesoterodine in comparison to that of placebo and 4 mg/day of tolterodine ER in the European Phase III study for the three co-primary end-points: number of micturitions (baseline 11.5 – 12.0/24 h across all groups), number of urgency incontinence episodes (baseline 3.7 – 3.8/24 h across all groups) and treatment responders (defined as 'greatly improved' or 'improved').
Adapted from [48].

was significantly more effective for most efficacy parameters than 4 mg/day in the pooled analysis of both Phase III studies [50]. Given the adverse effects of OAB on quality of life it also appears important that significant symptom improvements are detectable as early as 2 weeks after initiation of fesoterodine treatment, that is the earliest time point of assessment after randomisation [50]. In this context it is also relevant that several rating scales assessing patient reported outcomes and quality of life have shown dose-dependent and significantly greater improvements with fesoterodine than with placebo [52].

With regard to clinical end-points in the overall OAB population, comparisons among data sets obtained from different studies are problematic and only direct comparative studies allow reliable conclusions [1,3]. At present, one direct comparative study between fesoterodine and another muscarinic receptor antagonist exists, which is the four-armed Phase III study also including a patient group receiving tolterodine ER at 4 mg/day [48]. In that study 8 mg/day of fesoterodine was numerically superior to both 4 mg/day of fesoterodine and 4 mg/day of tolterodine ER with regard to efficacy, but also had more adverse events (primarily dry mouth). A subsequent *post hoc* analysis of this study, comparing maximum registered doses of both agents, reported that fesoterodine at 8 mg/day was also statistically superior to tolterodine ER at 4 mg/day for the primary end-point (the number of urgency incontinence episodes) as well as for several secondary end-points [53]. In contrast, the incidence of adverse events was almost identical with 4 mg/day of fesoterodine and tolterodine ER, allowing for a direct comparison of their efficacy. Fesoterodine at 4 mg/day performed numerically better than tolterodine ER at 4 mg/day across all efficacy parameters, but a statistical analysis of this comparison has not been reported. Therefore, the present data only allow the conclusion that, at a similar adverse event incidence, the efficacy of 4 mg of fesoterodine is at least as good as that of tolterodine ER.

7. Safety and tolerability

In the Phase III trials, adverse events were noted in 55% of the patients during placebo treatment in the US study, whereas the corresponding incidences were 61 and 69% with 4 and 8 mg/day of fesoterodine, respectively [47]. In the mainly European study these incidences were 38% with placebo and 50 and 58% with 4 and 8 mg/day of fesoterodine, respectively [48]. As expected for a muscarinic receptor antagonist, dry mouth was the most frequently reported adverse event but was rated as mild to moderate in most cases. In one Phase III study it was seen in 7, 16 and 36% of patients receiving placebo, 4 and 8 mg/day of fesoterodine, respectively [47], whereas in the other Phase III study it was seen in 7.1, 21.7 and 33.8% in the same groups (16.9% for 4 mg/day of tolterodine) [48].

The other reported adverse events during fesoterodine treatment were also qualitatively and quantitatively in the range of what has been reported with other modern muscarinic receptor antagonists [1].

Based upon recent concerns regarding the cardiovascular safety of drugs in general, a thorough study of the possible effects on QT intervals was performed [33]. This included parallel groups of 64 – 68 subjects each, who were treated for 3 days with 4 mg/day of fesoterodine, the highly supratherapeutic dose of 28 mg/day of fesoterodine, the active control moxifloxacin at 400 mg/day or placebo. Both the standard dose of 4 mg/day and the highly supratherapeutic dose of 28 mg/day did not provide any evidence of QT prolongation (e.g. QTc for 28 mg/day from 404.5 ± 16.7 to 400.1 ± 14.0 ms, with delta: -5.0 ± 7.9 ms). In comparison a similar study with tolterodine showed no effect on QTc at the recommended doses (2 × 2 mg/day) whereas a modest QTc prolongation (5.6 ± 2.1 ms) was seen at the supratherapeutic dose of 2 × 4 mg/day: while the authors considered that to be clinically irrelevant [27], others have questioned this interpretation [54].

8. Regulatory affairs

Based upon the accumulated preclinical and clinical data the EMEA granted marketing authorisation approval for fesoterodine in April 2007. A registration procedure with the US authorities is under way.

9. Conclusions

Taken together, the available Phase II and III data show that fesoterodine at 4 and 8 mg/day is effective in the treatment of OAB symptoms. The overall efficacy and tolerability are in the range of what has been reported with other muscarinic receptor antagonists. A major difference as compared to other drugs is a significant dose dependency of its efficacy. This could be related to the smaller variability in exposure to active drug (see above), which facilitates the detection of dose differences due to a smaller data scatter. Moreover, based upon its pharmacokinetic and metabolic profile, only small restrictions exist for the use of 4 mg/day of fesoterodine in special patient populations.

10. Expert opinion

Fesoterodine is a prodrug that acts principally via its active metabolite 5-HMT and is indicated for the treatment of OAB. In contrast to many other clinically available muscarinic receptor antagonists, the active metabolite of fesoterodine is formed by non-specific esterases independent of the cytochrome P450 system. This is associated with a less variable exposure to the active drug than tolterodine treatment. This could be particularly relevant in patients with low CYP2D6 activity. As a result of its reduced pharmacokinetic variability, together with even lower lipophilicity of 5-HMT than of tolterodine, fesoterodine may exhibit further reductions in the risk of CNS side effects. The efficacy and tolerability of fesoterodine in OAB treatment is at least as good as with tolterodine or other muscarinic receptor antagonists. Due to the cytochrome P450-independent formation of 5-HMT and its elimination via multiple pathways, both hepatic and renal, the standard 4 mg/day starting dose of fesoterodine can also be used in patients with impaired liver or kidney function and in those concomitantly receiving potent CYP3A4 inhibitors. This feature distinguishes fesoterodine from many other muscarinic receptor antagonists. Based upon the high prevalence of co-morbidities and co-medications among OAB patients, this profile could yield clinically relevant benefits.

Declaration of interest

Within the last 5 years the author has received research support, honoraria or other considerations related to OAB from the following companies: Astellas, Bayer, Pfizer, Schwarz and Theravance.

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