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REVIEW

Role of fesoterodine in the treatment of overactive bladder

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Abstract: Muscarinic receptors have long been the target receptors for treatment of patients with overactive bladder (OAB). These patients experience symptoms of urgency, urinary frequency and nocturia, with or without urge incontinence (the involuntary leakage of urine associated with urge). Fesoterodine, a pro-drug, structurally and functionally related to tolterodine, is the newest agent developed for the treatment of OAB. Fesoterodine is broken down to the active metabolite, 5-hydroxy-methyl-tolterodine (5-HMT) by non-specific esterases. This metabolism results in the complete breakdown of the parent compound and is responsible for dose related improvements in clinical efficacy and health related quality of life. Like other antimuscarinic agents including tolterodine, fesoterodine is associated with improvements in clinical variables related both to bladder filling (decreasing micturition frequency and increasing mean voided volume) and urgency (urgency and urge incontinence episodes). Improvements in health related quality of life following treatment with fesoterodine is indicated by improvements in 7 of the 9 variables measured by the King's Health Questionnaire. Also like other antimuscarinic agents, fesoterodine use is associated with adverse events including dry mouth. However the incidence of dry mouth is reduced with fesoterodine, compared to oxybutynin, due to the improved bladder selectivity of 5-HMT.

Keywords: fesoterodine, 5-hydroxymethyl-tolterodine, muscarinic, overactive bladder, urgency, incontinence

Overview of the overactive bladder

Overactive bladder (OAB) is a debilitating chronic disorder experienced by approximately 17% of both men and women over the age of 40 years, with the prevalence increasing with increasing age.[1,2] Patients with OAB typically experience symptoms of urgency, usually with frequency and nocturia, with or without urge incontinence (the involuntary leakage of urine associated with urge).[3] Results from the National Overactive Bladder Evaluation (NOBEL) Programme conducted in the US indicated that OAB was more prevalent than other chronic conditions such as heart disease, sinusitis, and asthma.[2]

OAB is a chronic disease with a major negative influence on quality of life, especially associated with the limitations it places on physical and emotional roles, vitality and social functioning.[4] The symptoms of OAB affect all aspects of life including: social (limiting outings due to frequent need to urinate), psychological (loss of self esteem associated with incontinence), physical (limitations of physical activities due to fear of incontinence) and occupational (decreased productivity).[3] OAB can also be associated with economic costs including; the personal costs of managing

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incontinence, the treatment costs associated with managing symptoms and providing care for incontinent nursing home residents and costs associated with decreased work productivity. In the US, the economic costs associated with OAB in the year 2000, were estimated to be between US$12.02 billion and US$17.5 billion.[5] This makes the economic impact of OAB, comparable to the economic impact of influenza, arthritis and osteoarthritis.[5]

The cornerstone symptom of OAB is urgency[1,6] which is defined as the complaint of a sudden compelling desire to pass urine which is difficult to defer.[3] This symptom is associated with frequency of urination and nocturia. Approximately 66% of patients with OAB do not have urge incontinence and are classified as OAB dry.[2] The remaining 33% of patients with OAB have urgency associated with incontinence and are classified as OAB wet.[2] Urodynamic testing demonstrates that patients with OAB wet have detrusor overactivity, where urine leakage arises from involuntary detrusor contraction.[3] The etiology of these involuntary detrusor contractions remains uncertain.

There are numerous treatment options available for patients with OAB including biofeedback, electrical stimulation, bladder training and pharmacotherapy, either alone or in combination. However, the primary treatment for the OAB is pharmacotherapy with muscarinic receptor antagonists[7–9] which have been used for many years. Oxybutynin (Ditropan®) was the first muscarinic receptor antagonist to be introduced to OAB therapy. Newer antimuscarinic agents include the M_3 selective antagonists, darifenacin (Enablex®) and solifenacin (VESIcare) and the relatively non-subtype selective antagonists, tolterodine (Detrol®) and its related compound fesoterodine (Toviaz®), which has only been recently introduced.

The role of muscarinic receptors in bladder physiology

The traditional dogma behind the treatment of OAB with muscarinic receptor antagonists was based on our understanding of the nerves controlling the physiological functions of the bladder. During filling the bladder detrusor muscle expands at low pressure. During this time the stretch of the bladder wall initiates the release of mediators (such as ATP) from the urothelium that signals bladder fullness via the underlying afferent nerves.[10] Signals from these afferent nerves are processed in the Pontine micturition centre in the brain and, at an appropriate time, efferent parasympathetic nerves are activated. The efferent parasympathetic nerves release acetylcholine onto muscarinic receptors located on the detrusor muscle.[11]

There are 5 individual subtypes of muscarinic receptors (M_1–M_5) that have been cloned and pharmacologically characterized.[12] In the urinary bladder, as in other smooth muscles, multiple muscarinic receptor subtypes have been identified.[13] Binding and immunoprecipitation studies,[14–17] have demonstrated that the majority of muscarinic receptors present in human detrusor muscle, are M_2 receptor (~70%) with smaller populations of M_3 (20%) and M_1 (10%) receptors.[17] Activation of muscarinic receptors by acetylcholine leads to contraction of the detrusor muscle and subsequent emptying of the bladder. Functional studies carried out in M_3 knockout mice[18] and human detrusor strips[19,20] have demonstrated that muscarinic M_3 receptors are the receptor subtype responsible for contraction of the detrusor muscle. Nevertheless, there is some evidence that M_2 receptors also have some functional importance.[21,22] Traditionally the muscarinic antagonists used to treat OAB were thought to inhibit activation of the muscarinic receptors responsible for detrusor contractions. Since both muscarinic M_2 and M_3 receptor subtypes are associated with detrusor contraction, muscarinic receptor antagonists, have been characterized according to their affinity for these receptor subtypes.

Antimuscarinic therapy for OAB

OAB therapy began when oxybutynin was shown to reduce contractions of the rabbit detrusor in response to the muscarinic agonist carbachol[23] although oxybutynin is not selective for any individual muscarinic receptor subtype (Table 1). Oxybutynin was then shown to be clinically effective at preventing detrusor spasms following transurethral surgery[24] which provided the impetus for antimuscarinic therapy for OAB. This was soon followed in the early 1980s with reports of oxybutynin providing symptomatic relief for patients with detrusor instability.[25,26]

In 1998 tolterodine, another muscarinic receptor antagonist was first introduced. Like oxybutynin, toltero-

Table 1 Range of Ki values (in nM) reported for antimuscarinic agents in cell lines expressing human muscarinic receptor subtypes

Compound	M_1	M_2	M_3	M_4	M_5
Oxybutynin[a]	4.5	36.5	3.3	5.2	19.6
Tolterodine[b]	6.9	6.7	6.4	6.8	5.9
Fesoterodine[c]	11.9	5.1	26.9	8.9	4.5
5-HMT[d]	5.9	5.6	5.7	5.8	6.1

[a]Data summarized from[36,85–89]
[b]Data summarized from[27,87–92]
[c]Data summarized from[36,92]
[d]Data summarized from[27,36]

dine, is relatively non-selective for individual muscarinic receptor subtypes (Table 1, Ki at M_3 and M_2 receptors of 6.4 nM and 6.7 nM respectively).[27] And also like oxybutynin, tolterodine is efficacious in the treatment of OAB.[28–32] However, the clinical efficacy of tolterodine has been demonstrated to be associated both with tolterodine itself, and with the generation of an active metabolite, 5-hydroxymethyl-tolterodine (5-HMT).[33–35] Like tolterodine, 5-HMT demonstrates similar affinity for the individual muscarinic receptor subtypes (Table 1 Ki at M_3 and M_2 receptors of 5.7 nM and 5.6 nM respectively).[27,36] The newest muscarinic antagonist for therapy of OAB is fesoterodine. Fesoterodine, which is structurally related to tolterodine, also results in the formation of the same active metabolite, 5-HMT[37,38] although the mechanism underlying production of 5-HMT are vastly different.

Pharmacokinetics of fesoterodine and tolterodine

The active metabolite of tolterodine, 5-HMT, is formed by cytochrome P450 2D6 (CYP2D6)[34] (Figure 1) which is subject to polymorphism.[39] The polymorphism of CYP2D6 is highly clinical relevant as it is responsible for variability in metabolism of more than 100 different drugs.[40] Based on their CYP2D6 phenotype patients are characterized as extensive metabolizers, if they have two functional CYP2D6 alleles, or poor metbaolizers who lack functional CYP2D6 alleles.[40] Up to 10% of white populations and 19% of black populations are characterized as poor metabolizers.[40] In patients classified as extensive metabolizers, 81% of the absorbed tolterodine, is extracted during first pass metabolism through the liver,[39] and hydrolyzed to 5-HMT with an average maximal plasma concentration of tolterodine and 5-HMT being similar (5.2 and 4.8 ng/mL respectively).[39] In contrast, in poor metabolizers only 18% of tolterodine is extracted during first pass metabolism through the liver[39] and the average maximal plasma concentration of tolterodine of is increased to 38 ng/mL while 5-HMT is not detectable.[39] Furthermore the concentration of 5-HMT released from metabolism of tolterodine is highly variable (1 to 100 ng/mL)[41] and this variability in the generation of the active metabolite makes individual tailoring of tolterodine dose necessary in some patients.[39]

Fesoterodine has been developed as a sustained release preparation with maximal plasma concentrations of 5-HMT detected approximately 4 to 6 hours after oral administration.[42] In contrast to tolterodine, the formation of the active metabolite from fesoterodine is not dependent on CYP2D6 activity (Figure 1) but rather occurs due to hydrolysis of fesoterodine

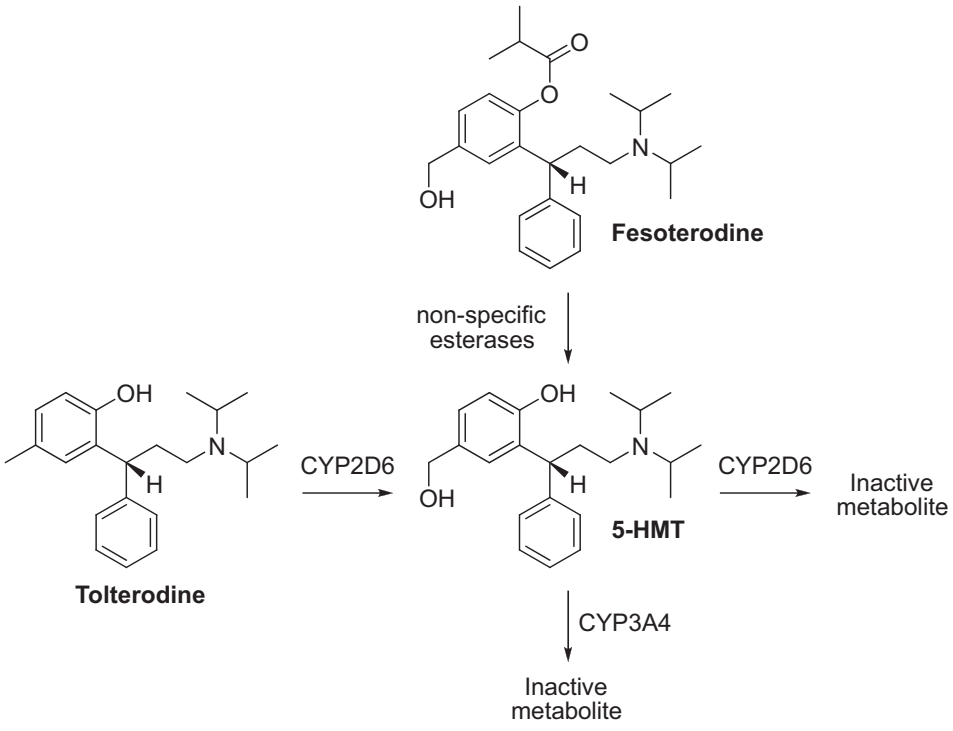

Figure 1 Metabolic pathways responsible for the generation of 5-hydroxymethyl-tolterodine (5-HMT) from tolterodine and fesoterodine.

by non-specific esterases. No fesoterodine is detected in the plasma of patients indicating that metabolism of fesoterodine is rapid and complete.[41,43] Also, in contrast to tolterodine, there is little inter-subject variability in the generation of 5-HMT from fesoterodine, as the activity of the non-specific esterases is similar in all people.[37,44] Oral administration of a single dose of 4 mg fesoterodine, results in a maximal plasma concentration of 5-HMT between 1 and 10 ng/mL,[41,45] with plasma concentrations of 5-HMT overlapping in patients characterized as extensive (0.9 to 5.6 ng/mL) or poor metabolizers (2.0 to 10.9 ng/mL).[41] In addition, plasma concentrations of 5-HMT increases linearly with increasing fesoterodine dose.[41] A large proportion of the active metabolite, 5-HMT, is transported in the plasma unbound (36 to 54%),[39,42] in contrast to tolterodine which is almost entirely bound to serum albumin (3.7% unbound).[39]

Breakdown of 5-HMT, generated from either tolterodine or fesoterodine, to inactive metabolites occurs via cytochrome P450 3A4 and CYP2D6 (Figure 1) and is therefore varied in extensive and poor metabolizers.[45,46] Approximately 70% of the fesoterodine dose is eliminated via the urine with approximately 16% being eliminated as 5-HMT[42] the rest as inactive metabolites.[43] The urine elimination of 5-HMT increasing proportionally with fesoterodine dose.[43] Excretion of 5-HMT is slowed in patients with renal impairment, however this delay in excretion was not associated with a significant increase in adverse events in these patients.[42]

Efficacy of fesoterodine and tolterodine in clinical trials

Both fesoterodine and tolterodine have been associated with clinical efficacy that exceeds placebo in a number of important clinical variables. Four recent randomized controlled trials have compared the clinical efficacy of fesoterodine with placebo,[37,47–49] two of which also compared fesoterodine with tolterodine.[47,49] Selected results from these clinical trials are summarized in Table 2. These results indicate that both fesoterodine and tolterodine have clinical efficacy against symptoms related to bladder filling (micturition frequency and mean voided volume) and urgency (urgency episodes, urge incontinence episodes).

In regards to symptoms related to bladder filling, treatment for 12 weeks with a once daily dose of fesoterodine (4 mg) resulted in a significant decrease in micturition frequency (5.5% greater than the average placebo effect) which corresponds to 1.7 less micturitions per 24 hours. Fesoterodine (4 mg) was also associated with an increase in mean voided volume of 25.1 mL compared to an average increase in placebo of 9.3 mL. These changes in clinical outcomes with 4 mg fesoterodine were comparable to tolterodine (4 mg) (Table 2).[47,49]

Fesoterodine was also effective against symptoms related to urgency. Treatment with 4 mg fesoterodine resulted in a significant decrease in urge incontinence episodes and urgency episodes. In OAB wet patients the decrease in urge incontinence episodes was 26.6% greater than the average placebo effect; that is 1.9 less episodes of urge incontinence per 24 hours (Table 2). In addition there was a significant decrease in urgency episodes which was 8.2% greater than the average placebo effect (Table 2). This corresponds to 2 less urgency episodes per 24 hours.[37,47–49]

One interesting feature of fesoterodine treatment is that the improvements in clinical efficacy are shown to be

Table 2 Efficacy of fesoterodine and tolterodine in 12 week clinical trials for OAB therapy

	Range of baseline values	Placebo[a,b]	Fesoterodine[a]		Tolterodine ER[b]
			4 mg	8 mg	4 mg
Micturition frequency	11.5–12.9	–9.3%	–15.5%*,†	–16.9%*,†	–15.6%*
MVV (mL)	150–160	+9.04	+23.0*,†	+33.2*,†,**	+25.1*
Urgency episodes	11–12.5	–7.5%	–16.9%*,†	–18.8%*,†	–17.5%*
UUI episodes	3.7–4.0	–40.7%	–67.5%*,†	–77.9%*,†,**	–56.3%
Continent days/week	0.6–0.8	+1.7	+2.6*,†	+3.0*,†,**	+2.6*

Notes: Statistical significance reported: *$P < 0.05$ vs placebo, †$P < 0.001$ vs placebo and **$P < 0.05$ vs 4 mg fesoterodine treatment.

Definition of measures:

Micturition frequency is the number of times a patient passed urine (including incontinence episodes) in a 24-hour period.

MVV is the mean voided volume (mL) per micturition determined from a 1-day collection period.

Urgency episodes is the number of times a patient recorded an urgency episode with or without incontinence per day determined from a 3-day bladder diary.

Urge urinary incontinence is the number of times the patient experiences involuntary leakage of urine accompanied by or immediately preceded by urgency in a 24-hour period determined from a 3-day bladder diary.

Continent days per week were normalized from a 3-day bladder diary.

[a]Data summarized from[37,47–49]

[b]Data summarized from[47,49]

increased with increasing dose (8 mg compared to 4 mg) (Table 2). Treatment with 8 mg fesoterodine resulted in a significantly greater decrease in urge incontinence episodes per 24 hours (9.1% greater than the average decrease with 4 mg fesoterodine), together with an increase in mean voided volume (8 mL greater than the average improvement with 4 mg fesoterodine). In addition, treatment with 8 mg fesoterodine was also associated with an increase in the number of continent days per week to 3.1 days compared to 2.7 days with fesoterodine 4 mg.[47–49]

Fesoterodine is unusual in showing this dose response relationship as a similar relationship has not been demonstrated for other antimuscarinic agents including tolterodine,[50–52] or the muscarinic M_3 receptors selective agents, darifenacin[53] and solifenacin.[54] It is likely that this dose response relationship is a result of the simple metabolism of fesoterodine by the non-specific esterases and the associated linear relationship between fesoterodine dose and plasma concentrations of the active compound, 5-HMT.[41,43]

In addition to the improvements in clinical outcomes fesoterodine has also been associated with improvements in Health Related Quality of life (HRQoL). The King's Health Questionnaire, which examines 9 domains related to quality of life,[55] has been used to assess improvements in HRQoL in people who suffer from OAB following 12 week treatment with fesoterodine.[56,57] Significant improvement in five or more domains of the King's Health Questionnaire is considered to indicate meaningful improvement in patient quality of life.[58] Similar to clinical efficacy, improvements in HRQoL were related to fesoterodine dose. Treatment with 8 mg fesoterodine showed significant improvements (compared with placebo) in 8 of the 9 domains assessed by the King's Health Questionnaire. While 4 mg fesoterodine (and tolterodine 4 mg), showed significant improvements (compared with placebo) in 7 of the 9 domains.[59] The domains where fesoterodine was associated with improvement include: severity/coping, emotions, role limitations, physical limitations, social limitations, sleep/energy, personal relationship and incontinence impact.[56,57] Of these improvements all except benefit for personal relationship were seen in patients who were classified as both OAB wet and OAB dry.[56] Treatment with 8 mg fesoterodine also showed significantly greater improvement compared to 4 mg fesoterodine in domains of severity/coping and emotions.[57]

Adverse events associated with fesoterodine and tolterodine

While muscarinic antagonists can be used to effectively treat OAB in approximately 65% of patients, numerous patients discontinue therapy long term due to adverse events including dry mouth and constipation.[59] These adverse events occur due to a lack of organ selectivity of antimuscarinic agents[60] as muscarinic receptors are not only located on the detrusor muscle but also in the salivary glands[61] and smooth muscle of the gastrointestinal tract.[13,62] The incidence of these adverse events in clinical trials of fesoterodine and tolterodine are summarized in Table 3.[37,47–49]

Dry mouth was the most common adverse event associated with fesoterodine use (Table 3), although most patients described it as mild to moderate. Twenty percent of patients being treated with 4 mg fesoterodine reported dry mouth.[37,47–49,63] This was increased to 35% in patients being treated with 8 mg fesoterodine[37,47–49] compared to an incidence of 6% in placebo (Table 3). Although common, dry mouth did not account for a large number of patients withdrawing from the 12 week clinical trials (Table 3). The incidence of dry mouth with fesoterodine (4 mg) was comparable to the incidence in patients treated with tolterodine (4 mg)[30,47,49,64] however it was considerably lower than that reported with oxybutynin (Table 3).[30,65]

The reason for the decrease in incidence of dry mouth with fesoterodine (and tolterodine) compared to oxybutynin may lie in the selectivity of 5-HMT for the bladder over the salivary gland (Table 4). Radiologand binding studies in

Table 3 Incidence of dry mouth and constipation in patients treated with oxybutynin, tolterodine, and fesoterodine

	Antimuscarinic dose	Dry mouth	Constipation	Discontinuation due to adverse events	Reference
Oxybutynin	5 and 10 mg	32.9%	7.3%	1.8%	Data summarized from[30,65]
Tolterodine ER	4 mg	19.8%	4%	2.5%	Data summarized from[30,47,49,64]
Fesoterodine	4 mg	20.2%	4.4%	5%	Data summarized from[37,47–49,63]
Fesoterodine	8 mg	34.7%	5.1%	6.8%	Data summarized from[37,47–49]
Placebo		4.9%	2.5%	3.1%	Data summarized from[37,47–49,65]

Table 4 Selectivity of antimuscarinic agents for bladder and salivary gland as determined by radioligand binding and *in vivo* functional studies

Compound	Radioligand binding studies		*In vivo* functional studies		
	Ki (nM)		ID_{50} (nmol/kg iv)[a]		
	Bladder	Salivary gland	Bladder	Salivary gland	Reference
Oxybutynin	9.8	3.02	215	76	Data summarized from[66,86,93]
Tolterodine	2.7	4.8	101	257	Data summarized from[66,90,91]
5-HMT	2.9	5.2	15	40	Data summarized from[27]

Note: data are not available for fesoterodine as it is completely metabolized to 5-HMT.
[a]ID_{50} determined from *in vivo* functional studies where antagonists were infused into anesthetized animals. Bladder contraction was stimulated by intra-arterial acetylcholine. Salivation was stimulated by electrical stimulation of the chorda-lingual nerve.[27,66,91]

salivary gland and bladder have demonstrated that oxybutynin has a three times higher affinity for salivary gland over the bladder (Table 4). In contrast tolterodine and 5-HMT have an affinity for the bladder that is twice that for the salivary gland (Table 4). Further to this, functional studies have examined the selectivity of oxybutynin, tolterodine and 5-HMT, for the bladder and salivary gland by comparing the concentrations required to inhibit detrusor contractions and salivation *in vivo*. Similar to the results from radioligand binding studies, oxybutynin inhibits salivation at a concentration that is approximately one-third lower than that required to inhibit bladder contraction (Table 4) indicating some degree of selectivity for the salivary gland.[66] In contrast, 5-HMT inhibits bladder contractions at a lower concentration than that required to inhibit salivation[27] indicating some degree of selectivity for the bladder. The reasons for this bladder selectivity of 5-HMT is unknown and cannot be explained simply by selectivity for individual muscarinic receptor subtypes.

Antimuscarinic agents show clinical efficacy against the symptom of urgency

Fesoterodine and tolterodine have demonstrated efficacy against symptoms of urgency as demonstrated by improvements in the clinical variables of urge incontinence episodes and urgency episodes per 24 hours (Table 2).[37,47–49,67] This is similar to reports from clinical trials with other muscarinic receptor antagonists, including the M_3 selective agent solifenacin[68–70] and trospium.[71] However, these beneficial effects, on the symptoms of urgency, raises the question as to how urgency is sensed, what receptors are involved and why antimuscarinic agents are effective against urgency. Answering these questions and understanding how these antimuscarinic agents are efficacious against urgency is important, as urgency is the cornerstone symptom for OAB and the symptom that patients identify as their most bothersome.[6]

Recent reviews have suggested that at therapeutic doses, muscarinic antagonists do not appear to inhibit bladder contractility,[8,72] and their activity is now thought to be during bladder filling to increase bladder capacity and to decrease urgency[8] actions not attributable to inhibition of muscarinic receptors located on the detrusor.

Radioligand binding studies in both pig[73] and human bladder[17] have demonstrated M_2 (70%) and M_3 (30%) muscarinic receptors in the bladder mucosa. Mucosal muscarinic receptors have also been demonstrated using molecular RT-PCR studies which demonstrate expression of mRNA for M_1, M_2, M_3, and M_5.[17,74,75] Immunohistochemical studies have localized muscarinic receptor immunoreactivity to the bladder urothelium[74–76] and to suburothelial myofibroblasts.[76,77] The role of these mucosal muscarinic receptors in bladder micturition remains unclear. However, they may represent a site of action for the muscarinic receptor antagonists used to treat OAB.

Recent, *in vivo* studies in rat bladder have demonstrated that intravesical administration of carbachol can induce detrusor overactivity,[78] where as intravesical instillation of muscarinic antagonists including oxybutynin,[79] tolterodine[80] and darifenacin[81] reduces stretch activated afferent nerve firing in rat bladder, an effect also seen following systemic administration of oxybutynin.[82] Furthermore, clinical efficacy has been associated, in patients with OAB, with intravesical instillation of oxybutynin[83,84] It is possible that following oral administration of fesoterodine or tolterodine the presence of the active metabolites, 5-HMT, in the urine as a result of urinary excretion is partly responsible for the clinical efficacy of these agents.

Conclusion

Fesoterodine is a pro-drug developed to produce the active metabolite, 5-hydroxy-methyl-tolterodine (5-HMT) via the actions of non-specific esterases. This metabolism of fesoterodine results in the complete breakdown of the parent

compound and is responsible for dose related improvements in clinical efficacy and health related quality of life. Fesoterodine, like tolterodine and other antimuscarinic agents, has been shown to have clinical efficacy for the treatment of patients suffering from OAB. Treatment with fesoterodine is associated with improvements in clinical variables related both to bladder filling (decreasing micturition frequency and increasing mean voided volume) and urgency (urgency and urge incontinence episodes). Fesoterodine is also associated with significant improvements in health related quality of life as indicated by improvements in at least 7 of the 9 variables measured by the King's Health Questionnaire. Fesoterodine, like other antimuscarinic agents, is associated with adverse events such as dry mouth and constipation. However the incidence of these adverse events is reduced compared, to the original muscarinic antagonist oxybutynin, due to the improved bladder selectivity of 5-HMT.

Disclosure

The author declares no conflicts of interest.

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