Fesoterodine (Toviaz): new option for overactive bladder

Steve Chaplin *MSc, MRPharmS and* ***Adrian Wagg*** *FRCP*

KEY POINTS

- fesoterodine (Toviaz) is a prodrug that is rapidly converted to the active metabolite of tolterodine, which is an antimuscarinic agent
- licensed for the treatment of OAB symptoms and shares the contraindications of other agents in its class
- available as prolonged-release 4mg and 8mg tablets (28, £29.03)
- dosage 4mg once daily, increasing to max. 8mg once daily if necessary; reassess after eight weeks
- in clinical trials, fesoterodine 4 or 8mg once daily reduced the mean number of micturitions per day by about 0.5-1.0 and the mean number of urge incontinence episodes by 0.8-1.3 compared with placebo
- an additional 20-30 per cent of patients reported their symptoms improved/very improved compared with placebo
- although fesoterodine has not been directly compared with tolterodine, its efficacy appears to be similar
- adverse effects are similar to those of other antimuscarinic agents, the commonest being dry mouth, headache and constipation
- for some outcome measures the 8mg dose appears to be more effective than the 4mg dose, offering flexibility in dosing

Fesoterodine, the prodrug of the active metabolite of tolterodine, has been launched in two strengths for the treatment of overactive bladder. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Adrian Wagg comments on its place in treatment.

Overactive bladder syndrome (OAB) is defined as urgency, with or without urge urinary incontinence, usually with frequency and nocturia. Current management guidelines for OAB in women recommend lifestyle change, pelvic floor muscle training for three months and bladder training for six weeks as first-line therapy.[1] If bladder training is ineffective, an antimuscarinic agent should be added and women should be counselled about the adverse effects.

The drug of first choice is immediate-release oxybutynin; if this is not tolerated, the alternatives are darifenacin (Emselex), solifenacin (Vesicare), tolterodine (Detrusitol), trospium (Regurin) and modified-release (Lyrinel XL) or transdermal (Kentera) oxybutynin. These drugs improve frequency, leakage episodes and quality of life with no evidence of clinically important differences in efficacy. Antimuscarinic adverse-effects are common.[2,3]

Propiverine (Detrunorm) is a further alternative to treat urinary frequency but not urge incontinence; intravaginal oestrogens are an option for OAB symptoms in postmenopausal women with vaginal atrophy.[1]

The technology

Fesoterodine (Toviaz) is a prodrug: it is rapidly and extensively hydrolysed in plasma to 5-hydroxymethyltolterodine (5-HMT), the active metabolite of tolterodine. 5-HMT is an antagonist at muscarinic receptors with no selectivity for receptor subtypes *in vitro*.[4]

Fesoterodine is licensed for the treatment of OAB symptoms – increased urinary frequency and/or urgency and/or urgency incontinence. It is formulated as a modified-release tablet for once-daily administration. Treatment should be initiated at a dose of 4mg per day and increased to a maximum of 8mg per day according to individual response. The full therapeutic

effect is apparent within two to eight weeks. Dose adjustment may be required in patients with impaired renal or hepatic function depending on the severity of impairment.

As with all antimuscarinic drugs caution must be exercised when the patient is undergoing concurrent treatment with drugs that inhibit hepatic CYP3A4 enzymes, *eg* clarithromycin, protease inhibitors, as this will increase plasma levels of 5-HMT (see SPC for details).

Fesoterodine has the same cautions and contraindications as other antimuscarinics.

Clinical trials

Two phase III randomised, double-blind, 12-week trials provide the key clinical data for fesoterodine. Both included patients (mean age 58, 80 per cent of whom were women) with OAB and averaging 12-13 micturitions and four urge incontinence episodes per day. Seventy-five to eighty per cent of patients reported incontinence. The mean duration of OAB was 8-10 years.

The primary end-points were the change, after 12 weeks' treatment, in the mean number of micturitions per 24 hours, mean number of episodes of urge incontinence per 24 hours and the treatment response, defined as the proportion of patients reporting their condition as improved or greatly improved.[4]

In a US study in 836 patients, fesoterodine significantly reduced the mean number of micturitions per 24 hours compared with placebo (by 1.61 at 4mg per day and 2.09 at 8mg per day *vs* 1.08 with placebo).[5] It also significantly reduced the mean number of urge incontinence episodes in 24 hours (by 1.65 and 2.28 *vs* 0.96 with placebo) and was associated with a significantly greater treatment response (64 and 74 *vs* 45 per cent with placebo).

Treatment with fesoterodine also increased the number of continent days per week (from a baseline of 0.6-0.7) by 1.3 with placebo and 2.3 and 2.8 with 4 and 8mg per day. The two doses of fesoterodine were not compared. Nineteen per cent of patients did not complete the trial, of whom one-third (of all treatment arms) withdrew due to adverse events.

A European study involving 1135 patients compared fesoterodine 4 or 8mg per day with placebo and included modified-release tolterodine 4mg per day as an active control to validate the study

design.[6] The principal results are summarised in Table 1.

Both doses of fesoterodine and tolterodine were superior to placebo; fesoterodine was not compared with tolterodine. All active treatments reduced the frequency of nocturia and overall urgency severity. Thirteen per cent of patients withdrew from the trial, of whom 24 per cent (from all treatment arms) did so due to adverse effects.

	Placebo	Fesoterodine 4mg/day	Fesoterodine 8mg/day	Tolterodine 4mg/day
reduction in micturitions/24h	0.95	1.76	1.88	1.73
reduction in urge incontinence/24h	1.14	1.95	2.22	1.74
treatment response	53%	75%	79%	72%
increase in number of continent days per week	2.1	2.8	3.3	2.5

Table 1. Efficacy of fesoterodine 4 and 8mg daily compared with placebo and tolterodine[6]

Adverse effects

In data pooled from clinical trials, adverse effects were reported by 50 per cent of patients assigned to placebo or tolterodine 4mg per day, and by 60 and 64 per cent of patients taking fesoterodine 4 or 8mg per day.[4] Discontinuation due to adverse effects occurred in 3 per cent of patients taking placebo, 5-6 per cent with fesoterodine and 3 per cent with tolterodine. In long-term nonblinded studies, the dose of fesoterodine was reduced from 8 to 4mg per day due to adverse effects in 12 per cent of patients.

The adverse effects associated with fesoterodine are typical of an antimuscarinic agent (see Table 2) and include dry mouth (placebo 8 per cent, fesoterodine 4mg per day 22 per cent, 8mg per day 35 per cent, tolterodine 17 per cent), headache (8, 8, 6 and 5 per cent respectively) and constipation (2, 4, 6 and 3 per cent).[4]

Data from ongoing long-term nonblinded studies suggest that most adverse effects occurred early during treatment with the exception of urinary retention, which occurred in 2-3 per cent of patients and was more common in men and older patients.

References

1. National Institute for Health and Clinical Excellence. *Urinary inconti-*

Adverse event	Placebo (%) (n=780)	Feso 4mg/day (%) (n=782)	Feso 8mg/day (%) (n=785)	Tolt 4mg/day (%) (n=290)
dry mouth	8	22	35	17
headache	8	8	6	5
constipation	2	4	6	3
urinary tract infection	3	3	4	1
dyspepsia	<1	2	3	2
lacrimal disorder (dry eye)	<1	1	3	<1
nausea	3	2	2	2
dry throat	<1	1	2	1
dysuria	1	2	2	1
abdominal pain, upper	1	1	2	1
nasopharyngitis	3	4	2	3
back pain	1	2	2	<1
diarrhoea	2	2	1	1
upper respiratory tract infection	2	2	1	<1
influenza	2	3	<1	<1
dizziness	2	2	1	1
abdominal pain	2	<1	<1	2
cough	2	2	1	2

feso = fesoterodine; tolt = tolterodine

Table 2. Adverse effects compiled from pooled data reported in primary safety trials (two phase II and two phase III) by ≥2 per cent of subjects in any treatment group; source: EPAR[4]

nence. Clinical Guideline No. 40. October 2006. www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf; accessed 17.7.08

2. National Collaborating Centre for Women's and Children's Health. *Urinary incontinence*. RCOG Press: London, October 2006 www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf; accessed 17.7.08.

3. Nabi G, Cody JD, Ellis G, *et al.* Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD003781. DOI: 10.1002/14651858.CD003781.pub2.

4. European Medicines Agency. *Toviaz European public assessment report*. June 2008. www.emea.europa.eu/humandocs/PDFs/EPAR/toviaz/H-723-en6.pdf; accessed 18.7.08.

5. Nitti VW, Dmochowski R, Sand PK, *et al.* Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007;178:2488-94.

6. Chapple C, Van Kerrebroeck P, Tubaro A, *et al.* Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol* 2007;52:1204-12.

By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

OAB is a common condition that has a significant negative impact upon quality of life for many people.[1] Treatment, according to published guidelines,[2-4] consists of lifestyle and behavioural techniques, adding in antimuscarinic therapy should these measures not achieve symptom improvement.

Fesoterodine is the prodrug of 5-HMT, the active metabolite of tolterodine. Unlike tolterodine, conversion to 5-HMT is by non-specific esterases rather than the cytochrome P450 system – although its elimination is still dependent upon this system. This may be clinically relevant – patients who do not respond to the licensed dose of tolterodine (4mg) or experience intolerable side-effects may have either had subtherapeutic or toxic doses of 5-HMT. This may be due to the variability in serum concentration of 5-HMT associated with the given 4mg dose.

Fesoterodine is also available as an 8mg dose, and for some outcome measures appears to be more effective than the 4mg dose.[5] Additionally, secondary analyses of available data show a favourable and clinically meaningful improvement on quality of life,[6] though the available data are limited and much evidence relies upon *post-hoc* analyses of clinical trials performed by the previous owner of the compound. More data are awaited.

Fesoterodine's side-effect profile appears much the same as other available antimuscarinics with the exception of a lower incidence of reported constipation; whether this is borne out in current trials and clinical use remains to be seen.

References

1. Coyne KS, Sexton CC, Irwin DE, *et al.* The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int* 2008; 101(11):1388-95.
2. European Association of Urology. *Guidelines in urinary incontinence.* www.uroweb.org/fileadmin/tx_eauguidelines/16%20Urinary%20Incontinence.pdf (accessed 18.8.08).
3. 3rd International Consultation on Incontinence. 2005. www.congress-urology.org/publishing/page.accueil.pub.html (accessed 18.8.08).
4.National Institute for Health and Clinical Excellence. *Urinary incontinence.* Clinical Guideline No. 40. October 2006. www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf.
5. Khullar V, Rovner ES, Dmochowski R, *et al.* Fesoterodine dose response in subjects with overactive bladder syndrome. *Urology* 2008;71 (5):839-43.
6. Kelleher CJ, Tubaro A, Wang JT, *et al.* Impact of fesoterodine on quality of life: pooled data from two randomized trials. *BJU Int* 2008;102(1):56-61.

By Dr Wagg, senior lecturer and consultant in geriatric medicine at University College London Hospitals and Camden PCT