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European Association of Urology

Fesoterodine: Individualised Treatment of Urgency Urinary Incontinence Across Patient Groups

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Article info

Keywords:
Fesoterodine
Incontinence
Muscarinic antagonists
Overactive bladder
Urgency urinary incontinence

Abstract

Context: Effective symptom reduction has the potential to significantly improve health-related quality of life (HRQoL) in patients with overactive bladder (OAB), particularly those experiencing urgency urinary incontinence (UUI).
Objective: To assess the evidence for flexible therapy with fesoterodine for patients with OAB, focussing on UUI.
Evidence acquisition: A nonsystematic search performed in 2010 was used to identify relevant literature regarding fesoterodine therapy.
Evidence synthesis: Antimuscarinic medications are the first-line pharmacotherapy for OAB, and tolterodine has been the treatment of choice for many patients. However, optimal efficacy may be difficult to achieve because of tolterodine's limited dosing options. Fesoterodine, a nonselective oral antimuscarinic with the same active metabolite as tolterodine, provides an alternative option. After oral administration, fesoterodine is rapidly and extensively converted into 5-hydroxymethyl tolterodine by ubiquitous, nonspecific plasma esterases, thus bypassing the hepatic cytochrome P450 pathway that mediates the metabolism of tolterodine. The superiority of fesoterodine 8 mg over tolterodine extended release (ER) 4 mg for the effective relief of UUI episodes and other OAB symptoms and improvements in HRQoL has been demonstrated in two superiority-design, head-to-head, randomised, placebo-controlled, clinical trials in patients with OAB and UUI. The majority of patients achieved dryness with fesoterodine 8 mg, a significantly higher percentage than with tolterodine ER 4 mg.

Clear dose-response relationships have been defined for fesoterodine in OAB patients for many outcomes, including UUI episodes, mean voided volume, continent days per week and self-reported treatment response. The dose-response magnitude for improving UUI episodes was larger in patients with greater UUI severity. Flexible dosing with fesoterodine appears to be well tolerated, with no unexpected safety signals during long-term treatment and high rates of patient-reported treatment satisfaction.
Conclusions: Flexible dosing with fesoterodine 4 mg and 8 mg allows for maximisation of treatment efficacy for a broad spectrum of patients with OAB.

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1569-9056/$ – see front matter © 2011 Published by Elsevier B.V. on behalf of European Association of Urology. doi:10.1016/j.eursup.2011.01.003

1. Introduction

Overactive bladder (OAB) is defined by the International Continence Society as a syndrome associated with symptoms of urgency with or without urgency urinary incontinence (UUI), which is usually accompanied by frequency and nocturia [1,2]. OAB is a prevalent condition, affecting up to 27% of men and 43% of women aged ≥40 yr [3,4]. In the population-based EPIC study of >19 000 individuals from Canada and Europe aged ≥18 yr, OAB was reported by 12.8% of women and 10.8% of men [5]. Among women and men with OAB who reported urinary incontinence, 23.8% and 41.6%, respectively, reported that their urinary incontinence was UUI only [5].

OAB symptoms have a significant negative impact on health-related quality of life (HRQoL), often leading to marked changes in lifestyle and daily activities, sleep quality, self-esteem, depression status, and sexual behaviour [6–8]. Patients who have OAB with UUI have significantly poorer HRQoL than those with OAB without UUI episodes [6,9].

2. Evidence acquisition

A nonsystematic search performed in 2010 was used to identify relevant literature regarding fesoterodine therapy.

3. Evidence synthesis

3.1. Management of overactive bladder

The goals of OAB management are to relieve bothersome symptoms and to improve patients' HRQoL. Initial management of OAB includes lifestyle modifications (eg, weight loss, dietary and fluid management) and bladder training [10]. Antimuscarinic drugs are the first-line pharmacotherapy for OAB, based on their significant clinical benefit and safety profiles [11–13]. Two large systematic reviews and meta-analyses of randomised controlled trials of antimuscarinics for OAB were published in 2008 [11,12]. Chapple et al determined that antimuscarinics were more effective than placebo and were not associated with a statistically significant increase in serious adverse events (SAEs) versus placebo [11]. Although measurement tools varied, the majority of treatments were associated with an improvement in HRQoL [11]. Novara et al found that extended release (ER) formulations have benefits for both efficacy and safety over immediate release formulations [12]. In clinical practice, antimuscarinic drug selection should be individualised, taking into account a patient's comorbidities and concomitant medications as well as the available dosages and safety profiles of the various agents [14].

3.2. Development of dose flexibility with fesoterodine

Fesoterodine is an oral, nonselective antimuscarinic that is rapidly and extensively converted by ubiquitous nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is also an active metabolite of tolterodine, another antimuscarinic drug for the treatment of OAB symptoms. However, tolterodine is only partially metabolised to 5-HMT, via the cytochrome P450 (CYP) 2D6 enzyme, meaning that tolterodine and 5-HMT both produce pharmacologic effects after oral administration of tolterodine. The ratio of tolterodine to 5-HMT varies due to differential levels of CYP2D6 metabolic activity between individuals (Fig. 1) [15]. Partially due to this variability in active drug exposure, tolterodine is available with only a single dosage of 4 mg daily [15].

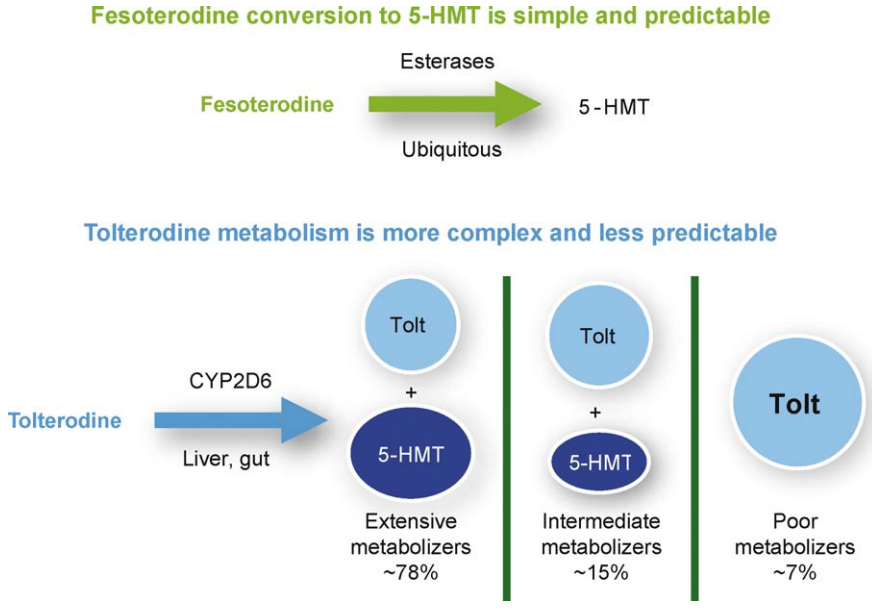

Fig. 1 – Esterase-mediated versus CYP2D6-mediated formation of 5-hydroxymethyl tolterodine. Reproduced with permission from Bentham Science Publishers Ltd Copyright 2010, from Malhotra B, Gandelman K, Sachse R, Wood N, Michel MC. The design and development of fesoterodine as a prodrug of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of tolterodine. Curr Med Chem 2009;16:4481–9 [15].
Tolt = tolterodine; 5-HMT = 5-hydroxymethyl tolterodine.