New perspectives of treatment with fesoterodine fumarate in patients with overactive bladder

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Abstract
Objective: To evaluate the effect of the treatment with fesoterodine fumarate in patients with overactive bladder, as an alternative in case of failure of the usual anticholinergic treatment, due to either lack of therapeutic efficacy or intolerance to side effects.

Material and method: A retrospective review of 158 patients with overactive bladder was carried out. The patients were divided into two groups: the first group consisting of 56 patients where the anticholinergic treatment was shown to be ineffective, and the second group; 102 patients who presented intolerance to anticholinergic side effects.

Results: For the first group where fesoterodine fumarate was used to improve effectiveness of the anticholinergics, improvement in the components of urinary urgency (p = 0.001), insufficient emptying (p = 0.001), incontinence (p = 0.009), and in the number of pads/day (p < 0.001) was detected. As to the second group where fesoterodine fumarate was used as an alternative to anticholinergics to avoid side effects, a high reduction in the incidence of dry mouth (p < 0.001) and constipation (p = 0.015) was seen, as well as a significant clinical improvement.

Conclusion: Fesoterodine fumarate is an optimal treatment option when the clinical response to anticholinergics has not been satisfactory, either by the lack of therapeutic action or by intolerance to side effects, and especially when the treatment is expected to be long.

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PALABRAS CLAVE
Fesoterodina; Intolerancia; Vejiga hiperactiva

Nuevas perspectivas de tratamiento con el fumarato de fesoterodina en pacientes con vejiga hiperactiva

Resumen
Objetivos: Valorar el efecto del empleo del fumarato de fesoterodina como rescate ante un tratamiento previo fallido con anticolinérgicos en pacientes con vejiga hiperactiva, por falta de efectividad terapéutica o por intolerancia a los efectos secundarios.

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**Introduction**

Overactive bladder is defined by a clinical picture consisting of symptoms of urinary urgency, with or without urinary incontinence, and usually associated to increased daytime urinary frequency and nocturia. Overactive bladder syndrome is an entity with a high incidence in our environment. It is estimated to affect 21.5% of the adult population over 40 years and about 30% of people over 75 years. Its incidence alone justifies its importance, more so if we consider that only 28.4% of the subjects with urinary symptoms compatible with overactive bladder are diagnosed. It is also a disease that negatively affects the quality of life, as 53% of the affected patients report that their symptoms are really annoying.

Successful treatment of overactive bladder symptoms depends primarily on the persistence with which it follows the prescribed medication, that is, the drug efficacy and the tolerability it offers. In this sense, anticholinergics are the first line treatment of overactive bladder.

We have appreciated that in routine clinical practice, inefficiency, and even more, intolerance to this type of drugs are frequent. This greatly impedes adherence by patients, implying an inability to control urinary symptoms.

Within this context, fesoterodine fumarate is the latest antimuscarinic drug released. Its great advantage is that it acts as a prodrug. After oral administration of the drug, this is rapidly and completely hydrolyzed by non-specific plasma esterases, leading to its active metabolite, 5-hydroxymethyl tolterodine, common active metabolite to that of tolterodine. Therefore, it is a drug that for its activation, it does not require first hepatic step. Despite this fact, it requires a proper hepatic metabolism, since its inactivation depends on CYP3A4 and CYP2D6 hepatic isoenzymes.

The active metabolite, 5-hydroxymethyl tolterodine, acts as a potent but non-selective inhibitor of muscarinic receptors, blocking the 5 receptor subtypes in the body. Its pharmacokinetics is dose proportional and, like its counterparts, its efficacy and side effects are considered to be dose dependent, but unlike tolterodine, it shows lower variability in concentration.

While it has been shown that fesoterodine fumarate can be as effective in controlling overactive bladder symptoms as the rest of anticholinergics of those previously employed considered uroselective, its efficacy versus placebo was assessed by 2 phase III, randomized, double-blind, placebo-controlled studies. On the other hand, the 8-mg fesoterodine has proved superior versus the 4-mg tolterodine and placebo in most of the aspects that include the overactive bladder by the results of 2 clinical, randomized, double-blind, placebo-controlled trials.

The studies to date support the start of treatment at escalating dose initiated from 4 mg, although it is true that in a high percentage (>50%) of patients it is necessary to double the dose to 8 mg, this being the one that really brings at least similar efficacy to commonly used anticholinergics.

On this basis we not only consider fesoterodine as a competitive drug as first-line treatment, but also we set ourselves the possible use thereof as rescue therapy before a previous ineffectual anticholinergic therapy, either due to lack of therapeutic response and poor control of symptoms or due to intolerance to the generated side effects.

**Material and methods**

We conducted a retrospective review of patients who started treatment with 8-mg fesoterodine fumarate every 24 h as rescue to a treatment with a previous anticholinergic, in a period of 18 months in our reference population. We included patients with symptoms compatible with overactive bladder, over 18 years, with clinic for at least 3 months, with daytime urinary frequency of at least 8 episodes a day and with at least 3 episodes of urgency a day, with or without urge or stress urinary incontinence, prior to any treatment implemented. On this review, we analyzed the initial clinical features, response to treatment, side effects, and therapeutic approach after drug administration.

The therapeutic response was assessed according to the OAB-Q SF questionnaire. This was broken down into 4 basic items that we consider basic as to the patient’s clinical history, in order to analyze more specifically the changes in the symptomatology. These were the urinary urgency...
component-urge urinary incontinence, the feeling of insufficient emptying after urination, the component of stress urinary incontinence, since a large percentage of these patients had mixed type incontinence, and the presence of dysuria or pain after urination. The assessment of urinary urgency and urge urinary incontinence merged into a single concept, since the vast majority of the times, in the usual anamnesis, we found it especially difficult to differentiate between a strong sense of urgency and urinary leakage preceded by episodes of urgency in patients with overactive bladder syndrome, mainly due to the remarkable intensity of symptoms for which patients were referred to our department. Each of these four items was assessed with a score of 0.1 or 2 according to the timing of presentation – 0: never, 1: isolated episodes throughout the week, 2: frequent episodes throughout the week. In turn, other clinical parameters were analyzed such as the number of daytime urinations, the number of episodes of nocturia, and the number of pads used per day. Similarly, the therapeutic outcome of the 3 months of treatment was found globally with the average of the total score of the OAB-Q SF (OAB V8 version) and Quality of Life: 1–5 (QL) questionnaires.

After a previous drug washout period of at least 10 days, the fesoterodine fumarate was administered for 3 months in doses of 8 mg orally every 24 h, time considered sufficient to achieve full therapeutic effect.

We performed a descriptive analysis of quantitative variables by mean, standard deviation and range, and frequency and percentage for qualitative variables.

We created 2 homogeneous groups of patients in terms of physical characteristics and personal history. In one of them we used fesoterodine fumarate as a rescue given the ineffectiveness of a prior anticholinergic, and in the other one as a rescue against intolerance. Therefore, the initial clinical features were different between both groups, as these are considered two cohorts of a general group of patients. The assignment of each patient to each group depended on the initial response to the previous treatment, proving unfavorable due to either ineffectiveness or intolerance to the prescribed drug.

We checked the normality of the distribution of the quantitative variables studied by the Kolmogorov–Smirnov test and then we examined the change of variables related to the therapeutic response: qualitative (urinary urgency, inadequate emptying, stress urinary incontinence, pain/dysuria and side effects) by means of before-after analysis using the McNemar test and quantitative clinical variables (number of daytime micturitions, number of nocturia episodes, and number of pads/day) using the T-test for paired samples.

The previously set significance level was 95% (p < 0.05). We used the SPSS v.15.0 program.

This study has the approval of the Ethics Committee of the Hospital Puerta del Mar, Cádiz, deciding in the same the absence of need for assessment by the Spanish Agency of Medicines.

Results

Characteristics of the study population

The total number of patients receiving fesoterodine fumarate as rescue therapy was 158. Group A was formed by 56 patients (35.44%), where fesoterodine fumarate was used as rescue from an inefficiency of a prior anticholinergic, and 102 (64.56%) were included in group B, where it was used against an intolerance.

All the patients were women screened in the Female Functional Urology and Urodynamics office at our hospital. The mean body mass index was 30.36 kg/m², indicating a considerable overweight population, bordering moderate obesity. The mean age of these patients was 64.66 years, with a mean of evolution of their symptoms of 7.89 years.

Regarding the surgical history, 34 patients (21.59%) had undergone surgery for hysterectomy and 21 (13.29%) corrective surgery for stress urinary incontinence. On physical examination, 37 patients (23.42%) associated the presence of a cystocele or anterior prolapse and 9 (5.69%) a rectocele or posterior prolapse.

All the patients were assessed by urodynamic study prior to treatment, in all cases demonstrating detrusor overactivity, which associated in 78 patients (49.36%) a lack of coordination or uncoordinated voiding, in most cases reflecting bladder-sphincter dyssynergia.

As a final diagnosis, the most common was mixed urinary incontinence in 69 patients (43.67%), followed by urge urinary incontinence in 65 patients (41.14%) and the urgency-frequency syndrome in 24 of these (15.19%). All the characteristics of the target population are summarized in Table 1.

Table 1  Characteristics of the study population.

<table>
<thead>
<tr>
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<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>N</td>
<td>158</td>
</tr>
<tr>
<td>Group A/ineffectiveness to previous AC</td>
<td>56 (35.44%)</td>
</tr>
<tr>
<td>Group B/intolerance to previous AC</td>
<td>102 (64.56%)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>30.36 kg/m²</td>
</tr>
<tr>
<td>Age</td>
<td>64.66 years</td>
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<tr>
<td>Clinical course</td>
<td>7.89 years</td>
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<tr>
<td>Surgical history</td>
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<tr>
<td>Hysterectomy</td>
<td>34 (21.59%)</td>
</tr>
<tr>
<td>Incontinence corrective surgery</td>
<td>21 (13.29%)</td>
</tr>
<tr>
<td>Cystocele</td>
<td>37 (23.42%)</td>
</tr>
<tr>
<td>Rectocele</td>
<td>9 (5.69%)</td>
</tr>
<tr>
<td>Urodynamic study</td>
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<tr>
<td>Detrusor overactivity</td>
<td>158 (100%)</td>
</tr>
<tr>
<td>Uncoordinated voiding</td>
<td>78 (49.36%)</td>
</tr>
<tr>
<td>Definitive diagnosis</td>
<td></td>
</tr>
<tr>
<td>Mixed urinary incontinence</td>
<td>69 (43.67%)</td>
</tr>
<tr>
<td>Urge urinary incontinence</td>
<td>65 (41.14%)</td>
</tr>
<tr>
<td>Urgency–frequency syndrome</td>
<td>24 (15.19%)</td>
</tr>
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</table>
Group A. Rescue fesoterodine fumarate for ineffectiveness of a previous anticholinergic (n = 56)

The most frequently used prior anticholinergic was 10-mg full-dose solifenacin every 24 h in 29 patients (51.78%). We also used 5-mg solifenacin every 24 h in 11 patients (19.64%) and 4-mg tolterodine every 24 h in 16 patients (28.57%).

Analyzing the results on the history of patients, we found a statistically significant improvement in terms of the urinary urgency component in the subgroup of 0 score, from no patients to 7 patients without any episodes of urgency (12.5%) (p = 0.001), and in subgroup 2 from 39 patients (69.64%) to 7 patients (12.5%) with frequent episodes of urgency (p = 0.001). Similarly, a positive favorable response was observed in terms of the feeling of insufficient emptying in groups 0 (no episodes), from 49 (87.5%) to 56 patients (100%) (p = 0.001), and 1 (isolated episodes), from 4 (7.14%) to no patients (0%) (p = 0.014). A striking effect was equally observed in terms of the stress of those patients with a diagnosis of mixed urinary incontinence in group 0 (no episodes), initially with 42 patients (75%), to 50 patients (89.29%) (p = 0.009). No statistically significant differences were found in terms of pain after urination or dysuria. Similarly, no differences were seen in the number of daytime urinations and the number of episodes of nocturia, and only one statistically significant difference was found in the number of pads used per day, going from 1.63 to 0.55 pads/day after treatment with the new anticholinergic (p < 0.001). In view of the results we can say that mainly the improvement achieved primarily affects the symptoms of urgency-incontinence, urge incontinence, and insufficient voiding or urgency. The therapeutic results are expressed according to the urinary symptoms in Fig. 1, and according to the clinical parameters in Fig. 2. The results in terms of the total score in the questionnaire were excellent. In the OAB-Q SF, an improvement from 27.39 to 8.71 points was appreciated after fesoterodine treatment (p < 0.001) and in the QL from 3.57 to 2.01 points (p = 0.037), data which combine the previously detailed results (Fig. 3).

Figure 1 Urinary symptoms in group A. Rescue fesoterodine fumarate due to ineffectiveness of a previous anticholinergic. † p < 0.02; ‡ p < 0.001; 2: frequent weekly episodes; 1: occasional weekly episodes; 0: no episodes.

Figure 2 Clinical parameters in group A. Rescue fesoterodine fumarate due to ineffectiveness of a previous anticholinergic. † p < 0.001.

Figure 3 OAB-QL SF questionnaires in group A. Rescue fesoterodine fumarate due to ineffectiveness of a previous anticholinergic. *p < 0.05; †p < 0.001.
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In terms of the tolerability expressed, an appearance of side effects previously absent in this group of patients was appreciated. The most frequent were dry mouth in 7 patients (12.50%) and episodes of acute urinary retention in 3 (5.38%). Dry mouth was slight and there was no need to withdraw the treatment. The retention events entailed bladder catheterization and treatment discontinuation. No other expected side effects were noted, such as constipation or headache in any of the patients (Fig. 4).

The treatment discontinuation rate was 16.07%. Of these 9 patients, 3 had episodes of acute retention (already mentioned above) and 6 stopped taking the drug in relation to the lack of clinical response.

After 3 months of treatment in 27 patients (48.21%), we chose to continue with the same anticholinergic, depending on the therapeutic results obtained. This fact conditions the acceptable adherence to the treatment of the new drug prescribed. In 10 patients (17.86%), we decided to change to another anticholinergic, in view of the lack of improvement and even worsening of the symptoms, or because of the intolerance of the side effects. These were patients who were initially treated with 4-mg tolterodine or 5-mg solifenacin, which after another failure with fesoterodine started treatment with full-dose solifenacin. Other therapeutic options were contemplated when the result with fesoterodine was unsatisfactory, such as the application of local estrogens in 6 patients (10.71%), hyaluronic acid instillations in 6 (10.71%), and type A botulinum toxin intravesical injections in 6 other patients (10.71%) (Fig. 5).

Group B. Rescue fesoterodine fumarate due to intolerance of a previous anticholinergic (n = 102)

The most frequently used prior anticholinergic was solifenacin in doses of 5 mg every 24 h in 64 patients (62.74%). In these patients, increasing the dose was not considered, since we would presumably obtain a dose-dependent response in terms of the adverse events reported. 10-mg solifenacin was also used every 24 h in 13 patients (12.74%), and 4-mg tolterodine every 24 h in 25 of them (24.50%).

Considering the data obtained from the assessment of the symptoms of the patients, there was a statistically significant improvement in terms of urgency in group 2 (frequent episodes), from 45 (44.1%) to 19 patients (18.63%)
(p < 0.001) to the sense of insufficient emptying, in groups 0 (no episodes) from 96 (94.12%) to 102 patients (100%) (p = 0.035), and in group 2 (frequent episodes) from 6 (5.88%) to no patients (0%) (p = 0.029). A favorable response was also observed in terms of the stress incontinence component in group 2 (frequent episodes), from 45 (44.11%) to 19 patients (18.63%) (p < 0.001) and to pain or dysuria in groups 0 (no episodes), 77 (75.49%), to 89 patients (87.25%) (p = 0.046) and 2 (frequent episodes) from 19 (18.63%) to 7 patients (6.86%) (p = 0.015). If we analyze the clinical parameters, the only one where a statistically significant difference is appreciated with respect to the initial values is the number of pads, decreased after treatment with fesoterodine, from 1.53 initially to 1.06 pads/day after fesoterodine treatment (p < 0.05). The therapeutic results are expressed according to the urinary symptoms in Fig. 6, and according to the clinical parameters in Fig. 7. With regard to the questionnaires, employed as synthesis markers of clinical response, an improvement in the OAB-Q SF was shown with a decrease from 19.29 to 11.46 points (p = 0.04) and in QL from 3.14 to 1.67 points (p = 0.024) (Fig. 8).

Undoubtedly, the most important analysis in this cohort was the study of the incidence of the side effects. These effects were reassessed 3 months after the treatment, appreciating a statistically significant reduction in the incidence of dry mouth – 64 patients (62.75%) initially, and 14 (13.72%) after treatment with fesoterodine (p < 0.001) – and of constipation – 19 patients (18.63%) originally, and 6 (5.88%) after treatment (p = 0.015) –, without observing changes in the rest of them (Fig. 9). It should be added that not only was the incidence of side effects reduced, but those observed were generally mild and well managed, with increased hydration of the patients and the use of non-astringent diets. Except for the 4 patients who had symptoms of acute urinary retention (3.92%), none was a cause of discontinuation of treatment afterwards.

The discontinuation rate was 7.84%, with 8 patients who did not continue the treatment, 4 of them due to episodes of urinary retention requiring bladder catheterization, and in other 4 patients in whom the therapeutic effect was not the expected one.

The therapeutic approach after 3 months of treatment in 51 patients (50%) was to keep the same scheduled anticholinergic. However, in 19 patients (18.63%), we chose reversion to the previous treatment. Of these 19 patients, 13 received treatment with 10-mg solifenacin, to whom the dose was reduced to 5 mg, and 6 were patients treated with 5-mg solifenacin with very mild side effects, mainly related to dry mouth, to whom symptomatological treatment was optimized. Local estrogen application was used as an alternative to treatment in 13 patients (12.74%), in the same proportion as intravesical instillations with hyaluronic acid (12.74%). Endoscopic bladder injections of type A botulinum toxin were used in 6 patients (5.88%) as a last line therapeutic measure (Fig. 10).

**Discussion**

In the first place, it is important to consider that the response to treatment with anticholinergics varies widely among patients due to the presence of individual agents. This could explain that an anticholinergic of more than proven efficacy may not be as effective in a particular group of preselected patients, which are favored by switching to another anticholinergic with a different chemical structure, as we observed in our series.

The pharmacokinetics of fesoterodine fumarate appears to play an important role in terms of the defense of its role as rescue medication in overactive

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**Figure 7** Clinical parameters in group B. Rescue fesoterodine fumarate due to intolerance of a previous anticholinergic. *p < 0.05.

**Figure 8** OAB-Q SF questionnaires in group A. Rescue fesoterodine fumarate due to intolerance of a previous anticholinergic. *p < 0.05.

**Figure 9** Side effects in group B. Rescue fesoterodine fumarate due to intolerance of a previous anticholinergic. †p < 0.02; ‡p < 0.001.
bladder. As described above, the fesoterodine is converted by nonspecific esterases into its active metabolite, 5-hydromethyl-tolterodine (5-HMT), which is also the active metabolite of tolterodine. These esterases do not show genotypic variations and they have not proved involved in any pharmacological interaction, unlike the hepatic cytochrome P450 2D6, responsible for the oxidation of 5-HMT tolterodine,\textsuperscript{17} or hepatic cytochrome P450 3A4, which is responsible for the metabolism of solifenacin in its 3 inactive metabolites, and its only active metabolite, the latter having a pharmacological activity similar to the parent compound, its concentration being lower.\textsuperscript{18} Therefore, the pharmacokinetic variability between individuals treated with fesoterodine is lower.

Despite all of this, we should remember some facts that are transcendent in the pathophysiology of overactive bladder and the mechanism of action of anticholinergics.

Under normal conditions, the detrusor muscle is under parasympathetic control and the primary stimulus is acetylcholine, acting on the muscarinic receptors. Such receptors are widely distributed throughout the body.\textsuperscript{16}

Recent in vivo studies indicate that the M2 and M3 muscarinic receptors increase proportionally to the scores related to the urgency and urinary frequency in patients with symptoms of urgency or overactive bladder.\textsuperscript{19}

The detrusor muscle contains all the subtypes of muscarinic receptors – M2 and M3 are the predominant ones – and subtype M2 exceeds the M3 at a ratio 3:1.\textsuperscript{20} However, the lower proportion of M3 receptors is the main responsible for normal urination, as it mediates the detrusor contraction.\textsuperscript{21}

M2 receptors may indirectly mediate the bladder contraction, increasing the contractile response to M3 receptors,\textsuperscript{22} or they may inhibit relaxation mediated by the sympathetic system.

The presence of M1 and M3 receptors has been demonstrated in the salivary gland, whereas the parotid glands mainly present M3 receptors. Salivation is mediated predominantly by the M3 receptors, which control both the volume and the high and low viscosity secretions.\textsuperscript{23}

In the human gastrointestinal tract, it seems that M2 and M3 receptors are the most important functionally.\textsuperscript{24} M2 receptors outnumber M3 ones at a ratio 4:1,\textsuperscript{24} but the M3 subtype mediates the cholinergic stimulation of the mobility of the gastrointestinal tract.\textsuperscript{25}

Some of the existing anticholinergic drugs defend uroselectivity over M3 receptors as the basis of its effectiveness and its low incidence of side effects. However, the M3 receptors not only play a key role at the bladder level, but they also do so at the level of the salivary or gastrointestinal glands, as we referred above. This could result in a hypothetical greater therapeutic efficacy on the overactive bladder symptoms of these ‘uroselective’ drugs, but in turn, in an increased incidence of side effects, particularly in the latter locations. It is possible that the absence of affinity for some sort of specific muscarinic receptor of fesoterodine, blocking the 5 receptor subtypes, along with reduced variability in the drug distribution in the body,\textsuperscript{26} can explain the low rate of dry mouth and constipation observed in the present study.

Being aware that these are only conjectures, and that the scientific basis of our study can become stronger, the results obtained in our review are striking. We have seen, according to our clinical practice, that the change of anticholinergic to an undesired effect to fesoterodine fumarate is most times clearly beneficial because of a really unknown mechanism; although it is true that this favorable change is more pronounced when there is intolerance to widespread antimuscarinic effects, as appreciated in group B.

The results in terms of side effects are favorable in both groups using fesoterodine rescue in this study. In group A, the data should be considered with caution. The results in tolerability are frankly biased because they were based on preselected patients, with good tolerance to anticholinergics and without a predisposition to side effects. On the other hand, in group B, the results in terms of tolerability were excellent, with significant improvements in symptoms as annoying as dry mouth, and generally this being of mild entity in the onset cases. It is important to consider that the fact of starting treatment on a preselected population of poor response or poor tolerance can significantly affect as a confounding factor to a significantly lower incidence to that described in the literature (28–35% dry mouth, 6–11% constipation).\textsuperscript{9,27} On the other hand, the data about the side effects are consistent with respect to the severity thereof, being in spite of the incidence described over other anticholinergics, such as 4-mg tolterodine, mostly mild and well tolerated.\textsuperscript{15}

The concept of the use of fesoterodine as rescue is not new. In a study published by Wyndaele et al.,\textsuperscript{27} conducted with 516 patients with overactive bladder and poor response to tolterodine, the change to fesoterodine meant a clear clinical improvement in the number of daytime micturitions, the number of episodes of urge incontinence, urgency, and nocturia, with 80% of patients stating satisfaction with treatment change. Our study extends the range of patients susceptible to fesoterodine rescue to any previous anticholinergic, not only tolterodine, analyzing the changes of efficacy and tolerability of the drug. Similarly, Castro et al.\textsuperscript{28} have recently published an observational study with 2038 patients with overactive bladder in which the clinical effect is described after the need for change of treatment with an anticholinergic to another (fesoterodine as rescue in 76.1% over other anticholinergics), either because of lack of clinical benefit (60%) or due to side effects (24%). In this study, 52% of the patients complied with the new treatment, 65.4% showed an improvement over the previous, 91% preferred it
to the previous one, and 93% reported that their symptoms had improved. These data corroborate our findings since the symptoms of overactive bladder initially treated with an anticholinergic, without good therapeutic response or poor tolerability, benefit from the change to a different anticholinergic, equally still without clarifying a specific reason for this phenomenon. It is remarkable that our study is more focused on the greater tolerability of the rescue medication in patients who had experienced secondary side effects (64.56%) than its use as a rescue to a low effectiveness of previous treatment (35.44%).

With regard to the start full dose, it is important to recognize that the recommended starting dose according to the technical sheet is 4 mg daily. Despite this, the dose of 8 mg is the one that has proved greater than 4 mg tolterodine and it is considered truly competitive. Furthermore, it should be the recommended one in individuals from a previous failure, where the therapeutic result is desired remarkable. The study by Wyndaele et al. supports this dose, since therein it was observed that 50% of the patients who started treatment at doses of 4 mg as rescue to a therapeutic failure of tolterodine we chose increase to 8 mg daily after one month of treatment.

Regarding the improvement of the component of stress urinary incontinence, it should be noted that the patients with a diagnosis of mixed urinary incontinence, while starting treatment with anticholinergics, were recommended hygiene and dietetic measures (reduction of caffeine consumption, reduced water intake, weight loss, regular exercise), along with exercises of pelvic floor rehabilitation, which remained from the start of the first treatment until at least 3 months after treatment with fesoterodine. On the other hand, the improvement of the component of stress incontinence is observed through a questionnaire, so that in part it may be due to a subjective appreciation, the same as it is sometimes difficult to ensure, in a urodynamic study, a stress urinary incontinence in an overactive detrusor substrate. We are aware that there are no studies that directly demonstrate the effectiveness of anticholinergics in the component of stress incontinence in mixed urinary incontinence (MERIT Study: Mixed Incontinence Effectiveness Research Investigating Tolterodine), but measurable improvement in the severity and frequency of the episodes of incontinence, the bladder capacity, and the quality of life indexes has been proved in various studies.

**Conclusion**

Fesoterodine fumarate is a proven-efficacy anticholinergic that provides one more treatment option for the symptoms of overactive bladder. However, it should be considered a valid treatment alternative if the results with another previous anticholinergic have been unsatisfactory.

The most striking information is that which shows that it can be used effectively as a rescue to an intolerance, in particular in reducing the incidence and severity of the annoying dry mouth and constipation, providing a possible solution if the drug treatment is prolonged.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**

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