The role of naftopidil in the management of benign prostatic hyperplasia

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Abstract: Naftopidil, which to a certain extent shows an affinity to α_{1D} -adrenoceptor subtype in addition to a high affinity to α_{1A} -adrenoceptor, has been used for the treatment of benign prostatic obstruction and benign prostatic hyperplasia (BPH) associated lower urinary tract symptoms (LUTS). The aim of the present review is to systematically refer to the published studies on this unique agent for BPH. Based on a randomized prazosin-controlled study and another double-blind placebo-controlled study, which verified the dose-dependent effects of naftopidil, the Japanese Ministry of Health, Labor and Welfare approved naftopidil for treating men with BPH in 1996. Several tamsulosin-controlled studies have suggested treatment effects of naftopidil similar to those of tamsulosin and potentially higher efficacy for alleviating storage symptoms by naftopidil. Although well-designed, randomized studies are warranted to confirm the long-term outcomes and effector/target of naftopidil, the α_{1A} -antagonist naftopidil, which also blocks α_{1D} -adrenoceptor, improves voiding symptoms, and may also be useful for the management of men with storage symptoms represented by nocturia, retrieving their quality of life impaired by BPH-associated LUTS.

Keywords: α_1 -adrenoceptor subtypes, benign prostatic hyperplasia, lower urinary tract symptoms

Introduction

Although the term benign prostatic hyperplasia (BPH) is defined based on histopathological diagnosis, it is currently regarded as a condition showing prostatic enlargement and lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO) [Hald, 1989]. LUTS, introduced in 1994, have been used to comprehensively represent symptoms of the lower urinary tract [Abrams, 1994]. LUTS consist of storage symptoms (daytime urinary frequency, nocturia, urgency, and urinary incontinence), voiding symptoms (slow stream, splitting or spraying, intermittency, hesitancy, straining, and terminal dribble), and postmicturition symptoms (feeling of incomplete emptying and postmicturition dribble) [Boyle *et al.* 2003]. While BPH-associated LUTS are common conditions in middle-aged and older men, LUTS impair the quality of life (QOL) [Boyle *et al.* 2003; Irwin *et al.* 2006; Girman *et al.* 1998]. Before the 1980s, endoscopic or open surgery was the therapeutic mainstay for the relief of BPO and LUTS. Since the

1990s, pharmacological therapy has played a critical role in the management of BPH, and α -adrenergic blockers/ α -adrenoceptor antagonists are currently the first-line treatment for BPH-associated LUTS.

Although the pathophysiology of BPH has not been fully elucidated, it is well known that antagonism of the α_{1A} -adrenoceptor subtype improves urinary symptoms with relaxation of the lower urinary tract; smooth muscle tone in the bladder neck, prostate, and prostatic urethra is mainly regulated by the α_{1A} -adrenoceptor. Approximately 75% of α_1 -adrenoceptors in the prostate show characteristics of the α_{1A} -subtype, and antagonists having a high affinity to α_{1A} -adrenoceptors such as tamsulosin hydrochloride have been developed to manage BPH [Walden *et al.* 1999]. However, naftopidil, which shows an affinity to the α_{1D} -subtype to a certain extent in addition to a high affinity to the α_{1A} -adrenoceptor, has also been used in clinical practice in limited nations [Takei *et al.* 1999]. Although details of the physiological mechanism

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of the α_{1D} -adrenoceptor and the pharmacological effect of naftopidil are still unclear [Kojima *et al.* 2009; Yamaguchi *et al.* 1997], recent experimental studies have suggested a role played by the α_{1D} -adrenoceptor subtype in bladder function during the storage phase as well as the regulation of detrusor contractility [Malloy *et al.* 1998; Chen *et al.* 2005]. The present review systematically refers to and summarizes the published studies on naftopidil in clinical practice to specify the role of this unique agent in the management of BPH.

Materials and methods

A PubMed search was performed for articles published until March 2012 based on the keyword naftopidil. Review articles were excluded, except for studies concerning statistics, meta-analysis, or reanalysis. We also referred to studies published in the Japanese language; many clinical trials on this agent have been conducted in Japan.

Results

Development of naftopidil

In the early 1990s, the pharmacological profile of naftopidil (development code KT-611) was established, with several studies using experimental and animal models. This drug was originally developed as an α -adrenoceptor antagonistic antihypertensive drug [Muramatsu *et al.* 1991; Peter *et al.* 1991]. Around the same time, a clinical trial was performed examining the treatment effects of oral naftopidil in patients with BPH. In 49 men with BPH, naftopidil significantly improved LUTS, reduced residual urine volume, and increased the average and maximum flow rates in uroflowmetry [Yamanaka *et al.* 1991]. The authors concluded that naftopidil is efficacious and safe for the management of men with BPH, and also suggested that its optimal dose ranged between 25 and 75 mg once a day. Subsequently, a double-blind prazosin-controlled study was conducted. The final study comprised 100 men in the naftopidil group and 98 in the prazosin group [Yamaguchi *et al.* 1992]. Although there was no difference in the improvement of LUTS, maximum and average flow rates, and residual urine volume between the two groups, the improvement rate of LUTS was seemingly higher in the naftopidil group (62.0%) than in the prazosin group (56.1%).

Additionally, the treatment efficacy and effect were assessed in some urodynamic studies. Yasuda

and colleagues studied 32 patients with BPO or BPH-associated LUTS who received naftopidil treatment (25–75 mg/day) [Yasuda *et al.* 1994]. The average and maximum flow rates increased ($p < 0.001$ in both groups), and residual urine volume and maximum urethral closure pressure were reduced ($p < 0.05$ in both groups). In their study, interestingly, the bladder capacity at the first desire point to void increased after treatment ($p < 0.05$). This observation suggested that naftopidil may have an impact on bladder function, as further supported by several following studies introduced in the next section. Based on the aforementioned prazosin-controlled study [Yamaguchi *et al.* 1992] and another double-blind, placebo-controlled study [Yamaguchi *et al.* 1997], which verified the dose-dependent effects of naftopidil, the Japanese Ministry of Health, Labor and Welfare approved naftopidil for treating men with BPO and BPH-associated LUTS in 1996. Naftopidil has also been approved for these indications in South Korea and China.

After approval of naftopidil for the management of benign prostatic hyperplasia: studies on dose-finding/optimal dose

Yokoyama and associates conducted a prospective, randomized controlled study to confirm the dose-dependent efficacy of naftopidil in clinical practice [Yokoyama *et al.* 2006]. They recruited 153 men using the following inclusion criteria: prostate volume of at least 20 ml, International Prostate Symptom Score (I-PSS) of at least 8, QOL index of at least 2, and nocturia of three or more frequent. Of these 153 men, 139 were eligible for assessing the efficacy. The 139 patients were randomized to one of two groups: the first group received 25 mg/day of naftopidil ($n = 72$) and the second group received 75 mg/day of naftopidil ($n = 67$) for 4 weeks. The two groups were similar in terms of prostate volume (mean 32 ml in both) and other variables. In both groups, the I-PSS improved at the endpoint with no significant intergroup difference. In the 75 mg/day group, all the domains in I-PSS improved, while the 25 mg/day group showed no improvement in the domain of straining. The voided volume, maximum flow rate, and residual urine volume improved in the 75 mg/day group, but the residual urine volume alone was improved in the 25 mg/day group. Intergroup differences were noted for voided volume and the maximum flow rate. Adverse events were similar between the two groups (3.9% in the 25 mg/day and 2.6% in the

75 mg/day group). Thus, naftopidil seemingly has a dose-dependent efficacy also seen in clinical practice after approval.

Oh-oka conducted a dose-comparison study in a unique setting. He started naftopidil treatment at the 75 mg/day dose and decreased the dose to 50 mg/day to verify the efficacy and safety of 75 mg of naftopidil and the possible changes in clinical effects following dose reduction [Oh-oka, 2009]. Based on the similar efficacy between the two doses, he concluded that the recommended dose of naftopidil should be 50 mg/day in Japanese men with BPH.

Funahashi and colleagues performed a study with dose escalation of naftopidil [Funahashi *et al.* 2011]. Their final study group comprised 122 men with BPO or BPH-associated LUTS, according to the following inclusion criteria: 50–80 years of age; I-PSS of at least 8 and QOL index of at least 2; prostate volume of at least 20 ml, and the maximal flow rate less than 15 ml/s. The efficacy of naftopidil was evaluated based on improvement in the I-PSS. Referring to American Urological Association guidelines, the authors defined men with improvement in I-PSS by 5 or more points as responders, and those with improvement in I-PSS of less than 5 points as nonresponders. All of the participants were first treated with naftopidil at a dose of 50 mg/day for 12 weeks, and nonresponders subsequently received 75 mg/day for 12 weeks. After the first treatment with 50 mg/day of naftopidil for 12 weeks, 64 patients (52.5%) were regarded as responders, and 58 as nonresponders. Thereafter, 40 of the 58 nonresponders were assessable following 12-week administration at 75 mg/day. After treatment with 75 mg/day, nine of these 40 patients (22.5%) reported improvement in I-PSS by 5 points or more compared with baseline. In their analyses, the baseline I-PSS and QOL index were different between 50 mg/day responders and nonresponders ($p < 0.001$ and $p = 0.048$, respectively), and this was also the case in each domain of the I-PSS except for urgency. Interestingly, the baseline uroflowmetry parameters did not differ between responders and nonresponders. Of 40 nonresponders proceeding to 75 mg/day, nine reported improvement with 75 mg/day treatment, and their prostate volume was smaller than that in the remaining 31 men without improvement ($p = 0.024$). For other variables at baseline, the pollakiuria score alone was lower in men with improvement on 75 mg/day than in those without improvement. The authors

concluded that dose escalation of naftopidil to 75 mg/day in men with BPH-associated LUTS is feasible in a proportion of patients, such as those without large prostate volume and severe pollakiuria.

Thus, the optimal dose of naftopidil has been determined according to the characteristics of each patient, such as the baseline I-PSS, prostate volume, responses, and adverse effects, and it is 50 or 75 mg/day in Japanese men in clinical practice. However, for men in the US or European countries, the optimal dose is estimated to be higher, and to apply the results of studies introduced in the following sections to them, an adjustment and consideration of limitations such as difference in the dose of tamsulosin in control arms are probably required.

After approval of naftopidil for the management of benign prostatic hyperplasia: the clinical effect profile possibly different from that of tamsulosin?

At the end of the 1990s and early 2000s, naftopidil was administratively approved for the treatment of BPO and BPH-associated LUTS in Japan, China and South Korea, and several comparative studies were published in various designs. Hayashi and associates compared the therapeutic efficacy of naftopidil and tamsulosin hydrochloride for treating BPH-associated LUTS [Hayashi *et al.* 2002]. They performed a crossover study. Eighty-five men without improvement in the QOL index on I-PSS using 50–75 mg/day of naftopidil for 4 weeks or longer subsequently received 0.1–0.2 mg/day of tamsulosin, and 89 showing no improvement in the QOL index using 0.1–0.2 mg/day of tamsulosin for 4 weeks or longer switched to 50–75 mg/day of naftopidil treatment. The I-PSS, maximum flow rate, residual urine volume, and adverse events were assessed at baseline and 8 weeks after switching. In the naftopidil-to-tamsulosin group, domains of urgency, slow stream, and straining significantly improved after 8 weeks of tamsulosin treatment compared with those on naftopidil before switching. In the tamsulosin-to-naftopidil group, domains of feeling of incomplete emptying, intermittency, and nocturia significantly improved 8 weeks after switching to naftopidil. These results suggested that naftopidil possibly has a different effect profile compared with that of tamsulosin.

Another randomized, controlled study comparing tamsulosin and naftopidil by Gotoh and associates concluded that the efficacy and safety of naftopidil are comparable to those of tamsulosin [Gotoh *et al.* 2005]. The inclusion criteria were a total I-PSS of at least 8, maximum urinary flow rate of less than 15 ml/s with a voided volume of at least 150 ml, and a prostate volume of at least 20 ml. Their final study group comprised 75 men in the tamsulosin group and 69 in the naftopidil group. Although not significant, prostate volume and the total I-PSS score at baseline tended to be larger/higher in the tamsulosin group than in the naftopidil group (mean 33.6 *versus* 29.0 ml, $p = 0.060$ and 17.1 *versus* 15.5, $p = 0.088$, respectively), and uroflowmetry parameters did not differ between the two groups. Patients in the tamsulosin group received 0.2 mg/day for 12 weeks, and those in the naftopidil group were treated with 25 mg/day for 2 weeks, and thereafter, 50 mg/day for 10 weeks. The I-PSS and uroflowmetry were assessed at baseline and 2, 4, 8, and 12 weeks after treatment. At the final evaluation, the IPSS, maximum flow rate, and residual volume improved in both groups, although the significance for residual volume improvement was borderline in the tamsulosin group. Improvement in these values was similar between the two groups. All of the IPSS domains improved in both groups at the final evaluation with no intergroup difference, and the time course and degree of the improvement in variables were also comparable between the two groups. Adverse effects were reported in nine of 95 (9.5%) men in the tamsulosin group and nine of 90 (10%) in the naftopidil group ($p = 0.94$). Interestingly, the profile of adverse events was seemingly different between the two groups. The tamsulosin group reported orthostatic dizziness in four, vertigo in one, severe headedness in two, and diarrhea in one, while the naftopidil group reported orthostatic dizziness in one, unsteady gait in one, numbness of the tongue in four, and abdominal pain in one. Systolic blood pressure significantly decreased in the tamsulosin group, and diastolic blood pressure decreased in both groups.

Ikemoto and colleagues also conducted a randomized, prospective study with a different crossover design [Ikemoto *et al.* 2003]. Ninety-six men with BPH, total I-PSS of 8 or higher, and maximum flow rate less than 12 ml/s were randomized to the naftopidil-to-tamsulosin group ($n = 43$) or the tamsulosin-to-naftopidil group ($n = 53$) (8-week initial to 8-week crossover

treatment). Two patients were withdrawn from each group because of adverse effects. The final study group comprised 31 men in the naftopidil-to-tamsulosin group and 34 men in the tamsulosin-to-naftopidil group. At baseline, the total I-PSS did not differ between the two groups (17.0 ± 1.1 and 17.5 ± 1.2 , respectively), and prostate volume, QOL index, maximum flow rate, and residual volume were similar between the two groups. In both groups, storage and voiding symptom scores were lower at the crossover point than at baseline, and they were also lower at the end of the study than at the crossover point. However, the difference in voiding score at the end of the study compared with at the crossover point in the tamsulosin-to-naftopidil group was not significant. The results were similar for the QOL index. The maximum flow rate and residual volume significantly improved at the crossover point and remained unchanged 8 weeks after crossover in both groups. The authors also performed subanalyses comparing each I-PSS domain before and after the initiation of naftopidil or tamsulosin. Data suggested that naftopidil was more efficient at improving storage symptoms such as pollakiuria, urgency, and in particular, nocturia. Another study performed around the same time with careful recording of frequency volume using a chart showed that naftopidil reduces nocturnal frequency (from 3.0 ± 0.8 to 2.5 ± 0.8 , $p < 0.001$) with voided volume increased (from 215.6 ± 91.2 to 247.8 ± 97.9 ml, $p < 0.01$) in 32 men with BPH-associated LUTS [Masuda *et al.* 2004]. These results also suggested that naftopidil is an interesting agent, which possibly improves BPH-associated storage symptoms.

After approval of naftopidil for the management of benign prostatic hyperplasia: studies on long-term consequences

Studies on long-term outcomes of men with BPH-associated LUTS receiving naftopidil have been limited. Although retrospectively, Kawachi and associates reported the long-term outcomes of naftopidil treatment [Kawachi *et al.* 2011]. They randomly selected 131 men with I-PSS of 8 or higher from clinical records; 78 and 53 patients were treated with naftopidil and tamsulosin, respectively. Age, prostate volume, uroflowmetry parameters, I-PSS, and the QOL index were equally distributed between the two groups, and the mean treatment duration was 2.7 years (range 1.5–3.4) in the naftopidil group and 2.5 years

(range 0.8–3.2) in the tamsulosin group ($p = 0.3156$). The overall 5-year treatment discontinuation rate was 38.1% (50/131), and the reasons for discontinuation did not differ between the two groups. These reasons included inadequate improvement (46.4%), adverse effects (21.4%), improved symptoms (10.6%), and unknown (17.9%). Factors predicting treatment failure were analyzed in 70 men in the naftopidil group. The 5-year failure rate was 54.0%. Men with a history of acute urinary retention had a higher failure rate than those without acute urinary retention ($p = 0.0014$). However, in the tamsulosin group, the presence of overactive bladder symptoms was a factor associated with treatment failure. These differences in long-term outcomes also suggest a difference in the effect profile between naftopidil and tamsulosin. Although experimental models could explain the association of the lower urinary tract functions with α_{1D} -adrenoceptor modulations [Chen *et al.* 2005], previous studies failed to give its clinical certification.

After approval of naftopidil for the management of benign prostatic hyperplasia: studies focusing on storage symptoms and quality of life issues

Takahashi and colleagues examined the treatment efficacy of naftopidil in men with BPH, focusing on overactive bladder symptoms [Takahashi *et al.* 2006]. They designed the study with inclusion criteria of urinary urgency at least once a day; total I-PSS of 8 or higher; and presence of any domain of pollakiuria, nocturia, or urgency of 3 or higher. The final study group comprised 81 men after one patient (1.2%) withdrew due to dizziness following the administration of naftopidil. Mean prostate volume was 29.6 ± 12.7 ml. Mean I-PSS and QOL index at baseline were 19.1 ± 6.0 and 4.6 ± 0.9 , respectively. Mean maximum flow rate and residual volume were 10.9 ± 4.9 ml/s and 48.3 ± 62.4 ml, respectively. In these patients, 6-week treatment with naftopidil reduced the total I-PSS from 19.1 ± 6.0 to 10.5 ± 6.5 ($p < 0.0001$), and the QOL index from 4.6 ± 0.9 to 3.2 ± 1.3 ($p < 0.0001$). All of the seven I-PSS domains decreased ($p \leq 0.0001$), and in particular, the domain for urgency improved significantly (3.1 ± 1.7 to 1.4 ± 1.6 , $p < 0.0001$). The results on uroflowmetry were comparable with those in previous reports. Yet, outcomes on the frequency volume chart were of note. Daytime and nocturnal frequency decreased from $9.3 \pm$

2.2 to 8.0 ± 2.3 ($p < 0.0001$) and from 2.7 ± 1.5 to 2.0 ± 1.3 ($p = 0.0009$), respectively, and voided volume increased from 174.0 ± 70.6 to 188.6 ± 64.3 ml ($p = 0.0453$) with no change in daily urine volume. Moreover, nocturnal frequency decreased in men without nocturnal polyuria (from 2.6 ± 0.9 to 1.9 ± 1.2 , $p = 0.0135$) as well as in those with nocturnal polyuria (from 3.5 ± 1.4 to 2.5 ± 1.2 ; $p = 0.0006$), suggesting naftopidil may also be effective for BPH-associated storage symptoms.

Oh-oka conducted a study focusing on nocturia [Oh-oka, 2008]. A total of 122 men with BPH, nocturia of three times or more frequent, and no improvement in nocturia, QOL index, and maximum flow rate after 6 weeks of tamsulosin treatment (0.2 mg/day taken in the morning) were selected. The mean prostate volume was 22.1 cm^3 (range 20.2–47.4). About 90% of the patients (107/122) were classified as having nocturia without polyuria showing reduced nocturnal bladder capacity. After a 1-week or longer washout period with placebo, the patients received 75 mg/day of naftopidil after dinner for 6 weeks. After conversion, the frequency of nocturia decreased from 3.1 ± 0.6 (range 3–5) to 1.2 ± 0.8 (range 0–2) ($p < 0.0001$) in addition to the decrease in daytime frequency (from 7.5 ± 1.9 to 6.9 ± 1.4 , $p = 0.0285$). Both storage and voiding I-PSS scores improved (from 5.4 ± 3.0 to 2.0 ± 1.8 , $p = 0.0006$ and from 7.7 ± 3.5 to 2.7 ± 2.1 , $p = 0.0006$, respectively). The QOL index improved in all patients (from 4.1 ± 0.8 to 1.5 ± 0.8 , $p = 0.0006$). Correspondingly, the voided volume increased (from 208.1 ± 81.0 to 237.4 ± 76.4 ml). The maximum and average flow rates also improved significantly. With pressure flow studies, the capacity at the first desire to void increased (from 148.3 ± 81.1 to 176.1 ± 76.9 ml), and the maximal cystometric capacity also increased (from 349.8 ± 122.7 to 381.8 ± 136.5 ml) showing borderline differences. Bladder compliance improved (from 16.8 ± 12.9 to 28.5 ± 17.9 ml/cm H_2O , $p = 0.0082$). Overall treatment success was observed in 85 of the 122 patients (69.7%). Accordingly, it is suggested that naftopidil is possibly effective in men with BPH who are bothered by storage symptoms represented by frequent nocturia.

Recently, Mizusawa and colleagues prospectively studied patients' preference/satisfaction with 50 mg/day compared with 75 mg/day of naftopidil, and analyzed differences in their background [Mizusawa *et al.* 2011]. Patients reporting

unsatisfactory improvement in LUTS with 50 mg/day of naftopidil for 4 weeks based on a question 'are you satisfied with your current urinary state, yes or no?' received 75 mg of naftopidil once a day for the next 4 weeks (75 mg group). Those having satisfactory improvement at 50 mg/day continued on the same dose (50 mg group). The final study group consisted of 46 men; 35 and 11 men were included in the 75 mg and 50 mg groups, respectively. At baseline, the score for slow stream alone was higher in the 75 mg group than in the 50 mg group (3.6 ± 1.6 versus 2.1 ± 1.9 , $p = 0.013$). The 75 mg group showed improvement in the I-PSS and QOL index in a time-dependent and dose-dependent manner (baseline versus 4 weeks after treatment, $p < 0.001$ in both; 4 weeks after treatment versus 8 weeks after treatment, $p = 0.019$ and $p = 0.003$, respectively). In the 50 mg group, the I-PSS and QOL index were reduced 4 weeks after treatment compared with those at baseline ($p = 0.004$ and $p < 0.001$, respectively); these measures were no different between 4 weeks and 8 weeks after treatment. The difference in QOL index (Δ QOL) during the initial 4 weeks with 50 mg/day treatment in the 75 mg group was smaller than that in the 50 mg group ($p = 0.045$). Among the I-PSS domains/items, change in nocturia (Δ nocturia) alone was smaller in the 75 mg group than in the 50 mg group ($p = 0.046$). With regression coefficient analysis, Δ nocturia was correlated with Δ QOL both in the 75 mg and 50 mg groups ($r = 0.437$, $p = 0.011$ and $r = 0.663$, $p = 0.036$, respectively). Although the authors did not perform urodynamic studies, these results suggested that a high score for slow stream at baseline and unsatisfactory improvement in nocturia with a low dose of naftopidil may be important factors for men with BPH-associated LUTS who prefer and benefit from dose escalation of this agent.

A previous report focused on health-related QOL (HRQOL) in men with BPH-associated LUTS receiving naftopidil. Awa and colleagues prospectively studied 56 men with BPH-associated LUTS [Awa *et al.* 2008]. Inclusion/exclusion criteria were similar to those of previous studies, and the dose was 50 mg/day. The authors referred to I-PSS and King's Health Questionnaire (KHQ). KHQ comprises nine domains and 21 questions and was used to assess LUTS [Kelleher *et al.* 2002]. Each I-PSS domain improved significantly after 12 weeks of treatment. KHQ scores in all nine domains decreased after treatment, and domains for incontinence impact, role limitations,

physical limitations, personal relationships, emotions, sleep and energy, and severity measures significantly improved. Interestingly, patients with overactive bladder symptoms showed significant improvement in all domains except for general health perceptions, while those free from overactive bladder had no improvement in any of the KHQ domains. These results also support the usefulness of naftopidil for treating men with BPH and storage symptoms, leading to improvement in QOL.

Komiya and colleagues performed a study on HRQOL in 99 men with BPH-associated LUTS receiving naftopidil [Komiya *et al.* 2010]. They assessed QOL using Short Form-8 (SF-8), an internationally validated questionnaire for HRQOL, consisting of eight domains: physical function (PF), role physical (RP), role emotional (RE), bodily pain (BP), general health (GH), vitality (VT), social function (SF), and mental health (MH) [Tokuda *et al.* 2009]. In their study, the dose of naftopidil ranged between 25 and 75 mg/day (96.9% received 50 mg/day or 75 mg/day). At baseline, the I-PSS and QOL index were correlated with each of the SF-8 domains (except for BP). The score for feeling of incomplete emptying was correlated with SF-8 RE, and the score for pollakiuria was correlated with SF-8 SF and RE. The score for urgency was correlated with SF-8 RP and SF, and other I-PSS scores also showed correlations with several SF-8 domains. Eight weeks after treatment, 71% of the patients continued treatment, 17.2% discontinued, and 11.1% were lost to follow up. SF-8 GH improved significantly at 4 weeks and further improved 8 weeks after treatment (47.5 versus 49.5 and 50.6). SF-8 VT also improved 8 weeks after treatment compared with that at baseline (from 50.3 to 51.6). The authors also showed that some domains in the participants impaired at baseline compared with those in the general population recovered to general levels after naftopidil treatment. These results suggest that naftopidil possibly retrieves QOL impaired by BPH-associated LUTS.

Relevant topics

Takeda and colleagues examined the efficacy and safety of naftopidil for treatment of neurogenic lower urinary tract dysfunctions [Takeda *et al.* 2011]. They prospectively studied 82 patients (40 men and 42 women) with neurogenic lower urinary tract dysfunction. After the stepwise administration of naftopidil for

10 weeks, pressure at maximum urinary flow rate decreased in men ($p < 0.05$), whereas it did not in women. Maximum flow rate increased in men ($p < 0.05$), but did not in women. Residual urine volume decreased both in men ($p < 0.01$) and women ($p < 0.05$), and the I-PSS decreased both in men and women ($p < 0.01$ in both). Thus, naftopidil has a significant effect on LUTS and some urodynamic parameters in both men and women with neurogenic lower urinary tract dysfunctions.

Ishizaka and colleagues studied the effect of naftopidil on the recovery of lower urinary tract functions after radical prostatectomy in men with localized prostate cancer [Ishizaka *et al.* 2009]. Although patients showed significant improvement in symptoms and uroflowmetry parameters, the efficacy of naftopidil was equivocal due to the short observation period (5 weeks) and absence of a control group. The utility of α_1 -adrenoceptor antagonists in the management of lower urinary tract disorder following focal therapy for localized prostate cancer is expected to attract greater interest with widespread minimally invasive surgery and brachytherapy [Tsumura *et al.* 2011]. Further studies on the role played by α_1 -adrenoceptor antagonists including naftopidil are warranted.

It is also known that α_1 -adrenoceptor antagonists are associated with ejaculatory dysfunction, and the mechanism of action and the relevance of α_1 -adrenoceptor subtypes are of interest in physiological and clinical practice. Masumori and colleagues studied the profile of ejaculatory disorders during BPH treatment with tamsulosin or naftopidil [Masumori *et al.* 2009]. They prospectively studied 95 men with BPO or BPH-associated LUTS. These men were randomized to naftopidil ($n = 48$) or tamsulosin ($n = 47$) therapy. Although the I-PSS and QOL index at baseline were lower in the naftopidil group than in the tamsulosin group (14.8 *versus* 17.5, $p = 0.049$ and 4.3 *versus* 4.7, $p = 0.005$, respectively), age, prostate volume, the maximum flow rate, and residual volume were similar between the two groups. Ejaculatory disorders could be evaluated in 45 men in the naftopidil group and 46 men in the tamsulosin group, and five (11.1%) and six (13.0%) men reported adverse events including ejaculatory disorders, respectively ($p = 0.999$). After excluding those who discontinued treatment due to circulatory adverse events, 27 of 40 (67.5%) in the naftopidil group and 24 of 37

(64.9%) in the tamsulosin group reported their sexual activity. Neither naftopidil nor tamsulosin treatment had any influence on the International Index of Erectile Function-5 (IIEF-5) score. Among assessable patients, two of 27 (7.4%) in the naftopidil group and four of 24 (16.7%) in the tamsulosin group reported abnormal feelings on ejaculation, although the difference was not significant ($p = 0.402$). The proportion of those who reported a reduction of the semen amount was higher in the tamsulosin group (26.9% *versus* 4.0%, $p = 0.0496$). Although further studies are required, naftopidil may possibly be associated with less frequent ejaculatory disorders.

Intraoperative floppy iris syndrome (IFIS), although rare, is problematic in cataract surgery, presenting with progressive intraoperative pupil constriction. Its overall incidence in cataract surgery is 2%, whereas it was reported to be encountered in 63% of men with BPH receiving the α_{1A} -adrenoceptor antagonist tamsulosin [Chang and Campbell, 2005]. Oshika and colleagues reported the prevalence of IFIS and the association between α_1 antagonists and IFIS in men undergoing cataract surgery [Oshika *et al.* 2007]. Of 1015 eyes of 762 men, IFIS was observed in 29 eyes of 25 men (overall incidence 1.1%), and all of them were receiving α_1 antagonists. The authors also studied a cohort comprising 110 men (134 eyes) treated with α_1 antagonists. Twenty-five of 58 eyes (43.1%) of 50 men receiving tamsulosin developed IFIS, while four of 21 (19.0%) eyes of 19 patients taking naftopidil had IFIS ($p = 0.042$). Although it is unclear whether the difference depends on the selectivity of these two agents for α_1 -adrenoceptor subtypes, naftopidil might be associated with less frequent IFIS.

Conclusion

The α_{1A} -antagonist naftopidil, which also blocks the α_{1D} adrenoceptor, improves voiding symptoms, and is possibly effective in treating men with BPH-associated storage symptoms represented by nocturia. Previous studies suggested that the α_{1D} -adrenoceptor subtype and the antagonism thereof might play a role in the regulation of bladder function and the relief of storage symptoms, respectively, although there is no clinical certification. To draw a definite conclusion for the usefulness of naftopidil, well-designed, randomized studies with long-term outcomes are needed.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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