INTERNATIONAL JOURNAL OF UROLOGY

International Journal of Urology (2011) **18**, 792–795 doi: 10.1111/j.1442-2042.2011.02850.x

Short Communication

Naftopidil *vs* silodosin in medical expulsive therapy for ureteral stones: A randomized controlled study in Japanese male patients

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Abstract: The aim of the present study was to compare the efficacy of the selective α_{1D}-adrenoceptor antagonist naftopidil and the selective α_{1A}-adrenoceptor antagonist silodosin (as an example) in the management of ureteral stones in Japanese male patients. A total of 74 patients with symptomatic ≤10 mm ureteral stones were enrolled in a prospective study and randomized into two groups: Group 1 received 50 mg naftopidil daily, whereas Group 2 received 8 mg silodosin daily. Patients were followed-up for up to 6 weeks. The primary endpoint was stone expulsion rate and secondary endpoints were stone expulsion time, the rate of interventions, such as transurethral ureterolithotripsy, extracorporeal shock wave lithotripsy, or ureteral stenting, and side effects. There were no significant differences between the two groups with respect to age, stone size, and location. The stone expulsion rate was 61% and 84% in the naftopidil and silodosin groups, respectively ($P = 0.038$). No significant differences were noted in stone expulsion time or the rate of interventions between the two groups. The findings suggest that α_{1A}-adrenoceptor blockade was clinically superior for stone expulsion our study population.

Key words: α-adrenoceptors antagonists, expulsive therapy, naftopidil, silodosin, ureteral calculi.

Introduction

Although minimally invasive treatments for ureteral stones, such as transurethral ureterolithotripsy (TUL) or extracorporeal shock wave lithotripsy (ESWL), are efficacious, they are not free of complications and are associated with high costs. Medical expulsive therapy (MET) using α-adrenoceptor antagonists (alpha-blockers) has recently emerged as an alternative strategy for the initial management of small ureteral stones.[1]

Sigala *et al*. found that the human ureter contained the different α_1-adrenoceptor subtypes, although the density of α_{1D}- and α_{1A}-adrenoceptors was significantly greater than that of α_{1B}-adrenoceptors *in vitro*.[2] Most of the studies on MET have used tamsulosin, a combination α_{1A}/α_{1D}-adrenoceptor antagonist, probably because of its excellent tolerability and the lack of a need for dose titration upon initiation of treatment. We have reported that low-dose tamsulosin significantly facilitates the spontaneous passage of ureteral stones.[3]

Naftopidil is a relatively selective α_{1D}-adrenoceptor antagonist,[4] whereas silodosin is a highly selective α_{1A}-adrenoceptor antagonist.[5] To examine the relationship between the distribution of α-adrenoceptor subtypes *in vitro* and clinical efficacy, we compared the effects of naftopidil and silodosin as MET to facilitate the passage of ureteral stones.

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Received 21 February 2011; accepted 17 August 2011.
Online publication 14 September 2011

Methods

From July 2007 to August 2008, and from October 2010 to December 2010, all Japanese male patients who presented with symptomatic ureteral stones, ≤10 mm in size, were recruited to the present study. The exclusion criteria were urinary tract infection (UTI), multiple stones, severe hydronephrosis, a solitary kidney, and current use of any type of alpha-blocker or calcium antagonist. The trial was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional ethics committee of the Tokyo Metropolitan Police Hospital. A total of 74 consecutive patients provided written informed consent to participate in the study.

Patients were randomly allocated to one of two treatment groups using a random number table envelope method. Group 1 received 50 mg naftopidil, one tablet daily in the morning, whereas Group 2 received 4 mg silodosin, two tablets daily in the morning and evening. Patients were evaluated with plain X-ray, ultrasonography, and unenhanced computed tomography (CT) when necessary. Stone size was calculated on the first plain X-ray or CT using a

Table 1 Demographic data of the two study groups

Characteristic	Group 1 (naftopidil)	Group 2 (silodosin)	*P*-value
Patients (*n*)	33	31	–
Mean (± SD) age (years)	44 ± 12	47 ± 11	0.19
Mean (± SD) stone size (mm)	4.6 ± 2.6	4.2 ± 1.9	0.47
Stone location (*n*):			
Right/left	14/19	19/12	0.13
Upper ureter	11	13	0.12
Middle ureter	4	0	
Lower ureter	18	18	

None of the differences were statistically significant.

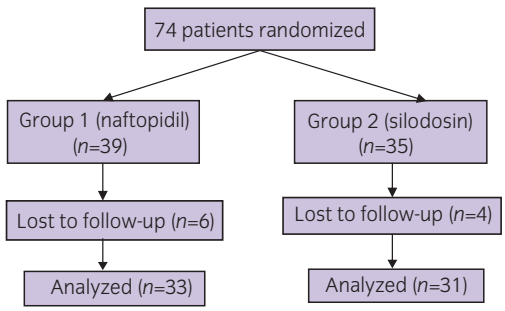

Fig. 1 Flow diagram of the study.

digital ruler. All patients were prescribed 50 mg diclofenac suppository on demand for pain relief. Patients were followed up biweekly with X-ray of the abdomen and ultrasonography and questioned about their symptoms to asses their level of pain, UTI, and any adverse events. The indications for intervention were uncontrollable pain or UTI during the follow-up period. Patients were instructed to record the date and time of stone passage. Follow-up was continued until the patient had been rendered stone free by intervention or spontaneous stone expulsion, confirmed by the patient himself, for a maximum of 6 weeks. The stone expulsion rate was the primary endpoint of the study. The expulsion time, defined as the number of days from random allocation until stone expulsion, and the intervention rate were also evaluated as secondary endpoints. Data were analyzed by Student's *t*-test and the Chi-squared test, as appropriate. All statistical analyses were performed using Microsoft Excel (Microsoft, Redmond, WA, USA). $P < 0.05$ was considered significant.

Results

Six patients in Group 1 and 4 patients in Group 2 were lost to follow-up, with 64 patients remaining for per-protocol analyses (Fig. 1). No significant differences were found between the groups with respect to age, stone size, or stone location (Table 1). Spontaneous stone expulsion was observed in 20 of 33 patients (61%) in Group 1 and in 26 of 31 patients (84%) in Group 2 ($P = 0.038$). Silodosin yielded a better stone expulsion rate than naftopidil, but there were no significant differences between the naftopidil and silodosin groups with regard to mean stone expulsion time (15 ± 12 *vs* 15 ± 9 days, respectively; $P = 0.87$) or intervention rate (21% *vs* 10%, respectively; $P = 0.052$; Table 2). No patients in Group 1 reported any side effects. One patient in Group 2 reported tachycardia as a minor side effect.

Discussion

Clinical studies have shown the efficacy of alpha-blockers in promoting the passage of distal ureteral stones since the first report in 2002.[7] A meta analysis with 911 patients showed that alpha-blocker therapy was associated with significantly increased rates of distal ureteral stone expulsion compared with conservative management alone, resulting in a 44% higher likelihood of expelling the stones. Most clinical trials have evaluated tamsulosin 0.4 mg, which is an α_{1A}/α_{1D}-adrenoceptor antagonist, without prior ESWL.[8] By way of example only, De Sio *et al*., Wang *et al*., and Yilmaz *et al*. reported better stone expulsion rates (81%, 79%, AND 90%, respectively) in patients who received 0.4 mg tamsulosin daily than in controls (54%, 53%, AND 58%, respectively).[9–11]

Unlike Western countries, low-dose (0.2 mg/daily) tamsulosin is widely used in Asian countries, including Japan. In a randomized controlled trial, both low and standard doses of tamsulosin increased the stone expulsion rate and decreased expulsion time compared with control in an Asian population.[12] Kobayashi *et al*. showed that low-dose tamsulosin decreased stone expulsion time following ESWL in Japanese male patients.[13] There have been relatively few studies in which other α_1-adrenoceptor antagonists have been used, including terazosin, doxazosin, alfuzosin, and naftopidil.[1,8] Wang *et al*., Yilmaz *et al*., and Agrawal *et al*.

Table 2 Results according to treatment

Endpoint	Group 1 (naftopidil)	Group 2 (silodosin)	*P*-value
Primary endpoint:			
Stone expulsion rate	20/33 (61%)	26/31 (84%)	0.039
Secondary endpoint:			
Mean (± SD) time to expulsion (days)	15 ± 12	15 ± 9	0.87
Intervention rate*	7/33 (21%)	3/31 (10%)	0.052

*Interventions included ureteral stenting, extracorporeal shock-wave lithotripsy, or transurethral lithotripsy.

demonstrated the efficacy of α_1-adrenoceptor antagonists in the management of lower ureteral stones regardless of the type of alpha-blocker used.[10,11,15]

To our knowledge, the present study is the first randomized controlled clinical trial to examine the effects of silodosin, a highly selective α_{1A}-adrenoceptor antagonist, which has 56-fold affinity for α_{1A}- over α_{1D}-adrenoceptors,[4] in the management of ureteral stones. Naftopidil is a relatively selective α_{1D}-adrenoceptor antagonist with approximately threefold stronger greater for α_{1D}- over α_{1A}-adrenoceptors.[5] Recently, Sun *et al*. demonstrated that naftopidil increased the stone expulsion rate compared with control.[14] In the present study, silodosin yielded a better stone expulsion rate than naftopidil. Our results suggest that silodosin is efficacious in the management of ureteral stones.

Many studies have been published on α_1-adrenoceptors in the human ureter since the first report in 1970. Malin *et al*. first described the presence of α- and β-adrenoceptors through the entire length of the human ureter and the physiological response (increased tone and frequency of contractions) of the ureter when exposed to α-adrenoceptor agonists.[6] In 2005, Sigala *et al*. found that α_{1D}- and α_{1A}-adrenoceptors were expressed in significantly larger amounts than α_{1B}-adrenoceptors in the human ureter.[1] These authors also demonstrated that the distal ureter expressed a greater amount of α_1-adrenoceptor mRNA than the proximal and medial ureter.

Itoh *et al*. reported that α_{1D}-adrenoceptor mRNA is more highly expressed than α_{1A}-adrenoceptor mRNA in each region of the ureter.[16] According to their results, an α_{1D}-adrenoceptor blocker can be expected to be more effective for the expulsion of ureteral stones than an α_{1A}-adrenoceptor blocker. However, Tomiyama *et al*. reported that, in the hamster ureter, ureteral contraction was mediated mainly by α_{1A}-adrenoceptors, even though α_{1D}-adrenoceptors were more prevalent.[17]

Our results indicate that an α_{1A}-adrenoceptor blocker is more effective than an α_{1D}-adrenoceptor blocker with respect to stone expulsion rate, suggesting more clinical usefulness of α_{1A}-adrenoceptor blockers.

Two limitations of the present study are its relatively small sample size and gender homogeneity. The study included only male patients because of restrictions regarding the use of naftopidil and silodosin in the Japanese insurance system.

In conclusion, silodosin (as an example of a selective α_{1D}-adrenoceptor antagonist) was more effective than naftopidil (as an example of a selective α_{1D}-adrenoceptor antagonist) with respect to stone expulsion rate for ureteral stones in Japanese male patients. Further studies on MET for ureteral stones are needed to determine the superiority of α_{1A}- *vs* α_{1D}-adrenoceptor blockers.

Conflict of interest

None declared.

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