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Short Communication

Efficacy of selective α1A adrenoceptor antagonist silodosin in the medical expulsive therapy for ureteral stones

Yasunori Itoh, Atsushi Okada, Takahiro Yasui, Shuzo Hamamoto, Masahito Hirose, Yoshiyuki Kojima, Keiichi Tozawa, Shoichi Sasaki and Kenjiro Kohri

Department of Nephro-urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan

Abstract: Recently, we reported that α1A adrenoceptor (AR) is the main participant in phenylephrine-induced human ureteral contraction. We therefore decided to carry out a prospective randomized study to evaluate the effects of silodosin, a selective α1A AR antagonist, as a medical expulsive therapy for ureteral stones. A total of 187 male patients, who were referred to our department for the management of symptomatic unilateral ureteral calculi of less than 10 mm, were randomly divided into two groups: group A (92 patients), who were instructed to drink 2 L of water daily, and group B (95 patients), who received the same instruction and were also given silodosin (8 mg/daily) for a maximum of 8 weeks. Expulsion rate, mean expulsion time and need for analgesics were examined. Overall, the mean expulsion time was 15.19 ± 7.14 days for group A and 10.27 ± 8.35 days for group B ($P = 0.0058$). In cases involving distal ureteral stones, the mean expulsion time was 13.40 ± 5.90 and 9.29 ± 5.91 days, respectively ($P = 0.012$). For stones of 1–5 mm in diameter, the mean expulsion time was 14.28 ± 6.35 and 9.56 ± 8.45 days, respectively ($P = 0.017$). For stones of 6–9 mm in diameter, the stone expulsion rate was 30.4% and 52.2% ($P = 0.036$), and the mean expulsion time was 21.00 ± 9.9 and 11.33 ± 8.31 days, respectively ($P = 0.038$). Herein, we report the first on silodosin in the management of ureteral lithiasis. Our findings suggest that silodosin might have potential as a medical expulsive therapy for ureteral stones.

Key words: medical expulsive therapy, selective α1A adrenoceptor antagonist, silodosin, ureteral stone, urolithiasis.

Introduction

Urolithiasis is a multifactorial disease that is often experienced in daily urological practice. Urolithiasis has been detected in 12% of the global population, although the number of patients is increasing, particularly in Western countries.[1,2]

The efficacy of minimally invasive therapies, such as shock wave lithotripsy (SWL), has been proven.[3] Nevertheless, SWL is not risk-free and is quite expensive. A watchful waiting approach can be used in a large number of cases. The use of a watchful waiting approach has been extended as a result of advances in pharmacological therapy, which can reduce symptoms and facilitate stone expulsion.[4,5] Several studies have shown that tamsulosin, an α1A/1D adrenoceptor (AR) antagonist, facilitates ureteral stone expulsion.[6–9]

Recently, we reported that α1A AR is the main participant in phenylephrine-induced ureteral contraction in the human isolated ureter.[10] Therefore, we decided to carry out a prospective randomized study to evaluate the effects of silodosin, a selective α1A AR antagonist, as a medical expulsive therapy for ureteral stones.

Correspondence: Yasunori Itoh M.D., Ph.D., Department of Nephro-urology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-Cho, Mizuho-Ku, Nagoya, Aichi 467-8601, Japan. Email: yasunori2009@gmail.com

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Methods

Patient population

A total of 200 male patients, who were referred to our department for the management of symptomatic calculi and had unilateral ureteral calculi of less than 10 mm in diameter, were considered for the present study. All stones were diagnosed with an unenhanced computed tomography scan. The exclusion criteria were urinary tract infection, severe hydronephrosis, diabetes, ulcers, hypotension, multiple stones or ureteral stricture. Of these, 187 male patients were randomly divided into two groups: group A (92 patients) who were instructed to drink 2 L of water daily and group B (95 patients) who received the same instruction and were also given silodosin (8 mg/daily) for a maximum of 8 weeks. The protocol for the research project was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Sciences, within which the work was undertaken, and it conformed to the provisions of the Declaration of Helsinki in 1995.

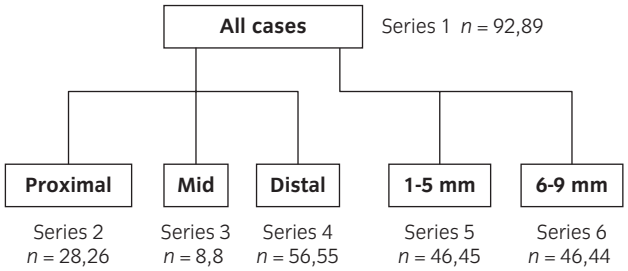

Fig. 1 Study design (*n* = group A, group B).

Informed consent was obtained from each patient. Randomization was only carried out with the patient's permission after they had read a summary describing the goals of conservative management and a description of the drugs they would be taking. The potential side-effects and complications of the drug were also discussed. Follow up was continued until the stone had been passed or intervention occurred. We examined the expulsion rate (%), mean expulsion time (days) and need for analgesics (times), and we also carried out an analysis in which we classified the subjects into six series according to their stone location and size (Fig. 1). Series 1 included all cases. Series 2 included cases involving proximal ureteral stones. Series 3 included cases involving midureteral stones. Series 4 included cases involving distal ureteral stones. Series 5 included stones of 1–5 mm in diameter. Series 6 included stones of 6–9 mm in diameter.

Statistical analysis

The Student's *t*-test or Mann–Whitney *U*-test was used to compare continuous variables between the two groups, and the χ^2-test was used for categorical variables. *P*-values less than 0.05 were considered to show significance.

Results

No statistically significant differences were found between the two groups with regards to age, mean stone size in diameter, stone location or stone composition (Table 1).

In all cases (series 1), the stone expulsion rate was 50.0% (92 patients) for group A and 66.3% (89 patients) for group B ($P = 0.056$), and the mean expulsion times were 15.19 ± 7.14 and 10.27 ± 8.35 days, respectively ($P = 0.0058$). Analgesics were required 1.7 ± 3.2 and 0.9 ± 3.8 times, respectively ($P = 0.172$).

In cases involving proximal ureteral stones (series 2), the stone expulsion rate was 53.5% (28 patients) for group A and 57.7% (26 patients) for group B ($P = 0.756$), and the mean expulsion times were 18.73 ± 8.66 and 13.45 ± 13.48 days, respectively ($P = 0.288$). Analgesics were required 2.2 ± 3.6 and 2.3 ± 6.6 times, respectively ($P = 0.524$).

Table 1 Patients' data

	Group A (control)	Group B (silodosin)	
n	92	89	
Mean age (years)	56.5 ± 10.1	57.2 ± 12.7	NS
Mean stone size (mm)	5.67 ± 2.10	5.69 ± 2.31	NS
Stone location			
Proximal	28	26	NS
Mid	8	8	
Distal	56	55	
Stone composition			
Calcium containing	82	80	NS
Uric acid	10	9	

NS, not significant.

In cases involving midureteral stones (series 3), the stone expulsion rate was 12.5% (8 patients) for group A and 50.0% (8 patients) for group B ($P = 0.244$), and the mean expulsion times were 21.0 and 8.67 ± 5.03 days, respectively (not significant). Analgesics were required 1.3 ± 2.1 and 0.1 ± 0.3 times, respectively ($P = 0.454$).

In cases involving distal ureteral stones (series 4), the stone expulsion rate was 55.6% (56 patients) for group A and 72.7% (55 patients) for group B ($P = 0.106$), and the mean expulsion times were 13.40 ± 5.90 and 9.29 ± 5.91 days, respectively ($P = 0.012$). Analgesics were required 1.5 ± 3.1 and 0.3 ± 0.9 times, respectively ($P = 0.382$).

For stones of 1–5 mm in diameter (series 5), the stone expulsion rate was 78.2% (46 patients) for group A and 80.0% (45 patients) for group B ($P = 0.941$), and the mean expulsion times were 14.28 ± 6.35 and 9.56 ± 8.45 days, respectively ($P = 0.017$). Analgesics were required 1.6 ± 3.2 and 1.5 ± 5.2 times, respectively ($P = 0.533$).

For stones of 6–9 mm in diameter (series 6), the stone expulsion rate was 30.4% (46 patients) for group A and 52.2% (44 patients) for group B ($P = 0.036$), and the mean expulsion times were 21.00 ± 9.90 and 11.33 ± 8.31 days, respectively ($P = 0.038$). Analgesics were required 1.7 ± 3.1 and 0.2 ± 1.1 times, respectively ($P = 0.151$).

Six patients in group B experienced side-effects (3 cases of retrograde ejaculation, and 1 case each of transient hypotension, nausea and difficult urination). They were excluded from the present study, because treatment could not be continued. There was no patient who required intervention in both groups within 8 weeks.

Any patients who were not stone free after 8 weeks of follow up (46 in group A and 30 in group B) were treated with SWL.

Discussion

Stimulation of the α1 AR is involved in the maintenance of ureteral tonus and resistance in mice, dogs and hamsters.[11–13] In urolithiasis patients, an α1A/1D AR antagonist, tamsulosin, facilitates spontaneous stone passage and reduces the time to expulsion of ureteral stones,[6–9] showing a close relationship between α1A/1D AR stimulation and ureteral contraction.

These clinical reports have molecular and pharmacological bases, as we reported that human ureter α1A and 1D AR are the most commonly expressed subtypes in real-time reverse transcription polymerase chain reaction and immunohistochemical staining.[14]

Recently, we reported that α1A AR is the main participant in phenylephrine-induced ureteral contraction in the human isolated ureter.[10] We found that the selective α1A AR antagonist, silodosin, was more effective than the selective α1D AR antagonist, BMY-7378, for noradrenaline-induced contraction in the human ureter.[15]

According to these results, we decided to carry out a prospective randomized study to evaluate the efficacy of silodosin as a medical expulsive therapy for ureteral stones.

It was reported that administration of tamsulosin in the medical management of proximal ureteral calculi can facilitate the spontaneous passage rate in stones <5 mm and the relocation of stones between 5 and 10 mm to a more distal part of the ureter.[16] Therefore, we carried out an analysis in which we classified the subjects into six series according to their stone location and size. There was no overall significant difference in the stone expulsion rate between the two groups. In series 6, group B showed a statistical advantage in terms of expulsion rate. In the European Association of Urology Guidelines on Urolithiasis, because of the high likelihood of spontaneous passage for stones up to approximately 5 mm, medical expulsive therapy is less likely to increase the stone-free rate because of the high spontaneous expulsion rate.[17] In series 1, 4, 5 and 6, group B showed a statistical advantage in terms of expulsion time.

This is the first study on silodosin on ureterolithiasis. We believe that silodosin might have potential as a medical expulsive therapy for ureteral stones.

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