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Short Communication

Silodosin and its potential for treating premature ejaculation: A preliminary report

Yoshikazu Sato, Hitoshi Tanda, Hisao Nakajima, Toshikazu Nitta, Keigo Akagashi, Tatsuo Hanzawa, Musashi Tobe, Kazunori Haga, Kosuke Uchida and Ichiya Honma

Department of Urology, Sanjukai Hospital, Sapporo, Hokkaido, Japan

Abbreviations & Acronyms
BPH = benign prostatic hyperplasia
CGIC = clinical global impression change
IELT = intravaginal ejaculatory latency time
LUTS = lower urinary tract symptoms
PE = premature ejaculation
PEP = premature ejaculation profile
SSRI = selective serotonin re-uptake inhibitors

Correspondence: Yoshikazu Sato M.D., Department of Urology, Sanjukai Hospital, Higashi Sapporo 2 Jo 3 Tyome, Shirosi-ku, Sapporo 003-0002, Japan. Email: ysato@sanjukai.or.jp

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Abstract: Premature ejaculation is a common sexual problem, as is erectile dysfunction. We evaluated silodosin, a highly selective α1A-adrenoceptor antagonist, as a new treatment option for premature ejaculation. α1-Adrenoceptor antagonists are widely used for lower urinary tract symptoms, and clinical studies on silodosin have shown excellent clinical efficacy for lower urinary tract symptoms. However, compared with other α1-adrenoceptor antagonists, silodosin appeared to suppress ejaculation in a relatively higher percent of trial participants. This suppression of ejaculation by silodosin suggested its potential for treating premature ejaculation. Consequently, we evaluated the feasibility of off-label silodosin as a new treatment option for premature ejaculation. Eight patients suffering premature ejaculation were treated with silodosin. Silodosin (4 mg) was given 2 h before sexual intercourse. Intravaginal ejaculatory latency time, premature ejaculation profile item, clinical global impression change in premature ejaculation and systemic adverse events were recorded. Intravaginal ejaculatory latency time was significantly prolonged (from 3.4 min to 10.1 min, $P = 0.003$). All patients answered better (much better) or slightly better for their own premature ejaculation problem compared with pretreatment condition in the clinical global impression change. Premature ejaculation profile also significantly improved. Two (25%), three (37.5%) and seven patients (87.5%) experienced anejaculation, reduced semen volume and discomfort during orgasm, respectively. However, these problems were not of major concern for the participants. No systemic adverse effects were reported. The current results support the possible use of silodosin as a new treatment option for premature ejaculation, and suggest that a placebo controlled study assessing its clinical usefulness would be worthwhile.

Key words: α1A-adrenoceptor antagonists, intravaginal ejaculatory latency time, premature ejaculation, silodosin, treatment.

Introduction

In addition to erectile dysfunction, PE is a common sexual problem.[1,2] Many epidemiological reports have shown that approximately 20–30% of men have complaints of PE.[3] As prevalence of IELT of 1 min is approximately 1–3%,[1,2,4] its prevalence varies widely depending on definitions of PE and the manner in which the prevalence data was gathered. PE is significantly related to high levels of distress, low satisfaction with sexual intercourse, and reduced sexual self-confidence and overall quality of life. For female partners, PE is a significant cause of distress.[1,2]

Treatment for PE has included oral medication, such as SSRI, topical agents and behavioral and cognitive therapy.[1,2] Recently, dapoxetine, a novel fast acting SSRI, was approved for the on-demand treatment of PE in several countries.[5,6] However, SSRI have possible SSRI-related adverse effects. Although, the safety and efficacy of some treatments for PE have been reported,[6] safer and more effective treatment options are still required.

α1-Adrenoceptor antagonists are widely used for LUTS associated with or without BPH,[7] but have some adverse effects, including postural hypotension and ejaculatory dysfunction.[8]

Table 1 IELT at baseline and post-treatment

	Baseline	Post-treatment	*P*-value
Median IELT min (range)	3.4 ± 2.2 (0.5–5)	10.1 ± 4.7 (5–15)	0.003

P-value was derived from statistical analysis by Student's *t*-test.

Table 2 Results of CGIC in PE

	Much worse or worse	Slightly worse	No change	Slightly better	Better or much better
Post-treatment	0	0	0	2 (25%)	6 (75%)

Q: Compared to the start of the study, would you describe your premature ejaculation problems as?

Silodosin is a new highly selective α1A-adrenoceptor antagonist, and clinical data show significant clinical efficacy for LUTS.[9,10] However, in these studies, abnormal ejaculation was found in a relatively higher percentage of participants.[10–12] This suppression of ejaculation by silodosin has been confirmed in well-designed studies with volunteers.[13,14] Furthermore, safety even for the elderly was well established in treatment data for LUTS.[10] These observations suggest that silodosin might be effective treatment for PE, and in this preliminary study, we evaluated off-label silodosin as a new treatment option for PE.

Methods

Eight heterosexual men with PE were enrolled in the present study. All patients met the following PE criteria, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DMS-IV-TR):[15] "persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it", which is associated with "marked distress and interpersonal difficulty." Participants had a mean age of 54.2 years (range 32–72 years) and reported having had PE for an average of 9.1 years (range 5–15 years). Six patients (75%) suffered from ED and had received treatment by phosphodiesterase type 5 inhibitors. All patients achieved adequate penile rigidity before participating in the present study.

Baseline and after treatment ejaculatory profiles were evaluated with the PEP Items[16] and IELT, measured using a watch (not a stop watch) by the patient. IELT refers to the time between the start of vaginal intromission and the start of intravaginal ejaculation or sense of orgasm. Patients' satisfaction for the treatment was evaluated by CGIC in PE.[17] Discomfort on orgasm and reduced semen volume or complete loss of projectile ejaculation (anejaculation) and ejaculation-related problems during administration of silodosin were evaluated by the same questionnaire used in a previous study.[14]

Then, 4 mg of silodosin was given 2 h before planned sexual intercourse with or without phosphodiesterase type 5 inhibitors. All patients tried sexual intercourse at least three times using silodosin during the 2-month treatment period. Mean IELT with silodosin during the treatment period was applied as a post-treatment value.

We informed participants that reduced semen volume or anejaculation were possible adverse events before starting treatment. All patients provided written informed consent. During the study, drug medication remained unchanged in all patients. The present study was approved by the ethics committee of our institution.

Results of ejaculatory status and the changes of parameters were tested using Student's *t*-test and χ^2-test. Statistical analysis was carried out using Stat View 5.0 for Windows (SAS Institute, Cary, NC, USA).

Results

IELT and satisfaction rate

The mean average of IELF was significantly prolonged (from 3.4 min to 10.1 min, $P = 0.003$; Table 1). A total of 75% of the patients reported improved or greatly improved symptoms, and 25% patients reported slightly improved PE problems after treatment by CGIC in PE (Table 2).

Premature ejaculation profile

Ejaculation control

No patients reported "good" or "very good" as baseline ejaculation control. All patients answered "good" or "very good" after treatment. Ejaculation control was significantly improved ($P = 0.003$).

Table 3 PEP at baseline and post-treatment

	Ejaculation control					*P*-value
	Very poor	Poor	Fair	Good	Very good	
Baseline	4 (50%)	3 (37.5%)	1 (12.5%)	0	0	0.003
Post-treatment	0	0	0	5 (62.5%)	3 (37.5%)	
	Satisfaction with intercourse					*P*-value
	Very poor	Poor	Fair	Good	Very good	
Baseline	2 (25%)	4 (50%)	2 (25%)	0	0	0.017
Post-treatment	0	0	2 (25%)	4 (50%)	2 (25%)	
	Personal distress					*P*-value
	Not at all	A little	Moderately	Quite a bit	Extremely	
Baseline	0	0	3 (37.5%)	3 (37.5%)	2 (25%)	0. 010
Post-treatment	0	6 (75%)	2 (25%)	0	0	
	Difficulty in relationship with partner					*P*-value
	Not at all	A little	Moderately	Quite a bit	Extremely	
Baseline	1 (12.5%)	4 (50%)	2 (25%)	0	1 (12.5)	0.506
Post-treatment	3 (37.5%)	4 (50%)	1 (12.5%)	0	0	

P-value was derived from statistical analysis by χ^2-test.

Satisfaction with sexual intercourse

Six patients (75%) reported "very poor "or "poor" satisfaction with intercourse at baseline. Six patients (75%) reported "good" and "very good" after treatment. Satisfaction with sexual intercourse was significantly improved ($P = 0.017$).

Ejaculation-related personal distress

All patients rated ejaculation-related personal distress more than "moderately" at baseline. Six (75%) patients reported "a little" for ejaculation-related personal distress after treatment. Ejaculation-related personal distress significantly decreased.

Difficulty in relationship with partner

Four (50%) patients reported "a little" for difficulty in relationship with partner at baseline, even though they had PE-related problems. In contrast to other problems, there were no significant changes in relationship difficulties with partner (Table 3).

Orgasm and ejaculatory discomfort

Discomfort at ejaculation

Six (75%) and one (12.5%) patients felt slight or moderate discomfort at ejaculation during treatment.

Bothered by ejaculatory discomfort

However, all patients reported "no problem" or "small problem" for discomfort at ejaculation.

Semen volume

Two (25%) patients reported "anejaculation" (no projected ejaculation with orgasm). Three (37.5%) patients experienced decreased semen volume.

Bothered by decreased semen volume

Three (37.5%) and five (62.5%) patients reported "no problem" and "small problem". Decreased semen volume was not a significant problem for the patients (Table 4).

Systemic adverse events

No symptomatic adverse events, such as postural hypertension were reported.

Discussion

The present preliminary study shows the potential of off-label silodosin as a new treatment option for PE. Our primary finding was the alleviation of PE in all patients with "on-demand" use of silodosin. All patients responded with

Table 4 Answers to the questions about ejaculatory discomfort during orgasm and volume of semen with silodosin treatment

Q1. Did you have a somewhat uncomfortable feeling during orgasm when you ejaculated?				
Not at all	Slightly	Moderately	Very	
1 (12.5%)	6 (75%)	1 (12.5%)	0	
Q2. How much has a feeling of some discomfort during orgasm been a problem for you?				
No problem	Small problem	Moderate problem	Big problem	
5 (62.5%)	3 (37.5%)	0	0	
Q3. How is volume of semen when you ejaculate?				
Normal	Slightly decreased	Very decreased	Not at all	Unknown
1 (12.5%)	1 (12.5%)	2 (25%)	2 (25%)	2 (25%)
Q4. How much has the volume of semen been a problem for you?				
No problem	Small problem	Moderate problem	Big problem	
3 (37.5%)	5 (62.5%)	0	0	

better (much better) or slightly better for their PE problem compared with their pretreatment status in the CGIC. IELT and PEP also significantly improved. In accord with these improved parameters, PE-related distress was significantly reduced.

There is supporting data for the application of silodosin to the suppression of PE. Suppression of ejaculation by silodosin and other α1-adrenoreceptor antagonists was reported as an adverse effect in clinical studies of their use in LUTS.[7,10–12] Kobayashi and Hisasue confirmed suppressive actions on ejaculation of silodosin and tamsulosin in volunteers; the authors proposed that the suppressive actions of α1-adrenoreceptor antagonist was a result of inhibition of seminal emission, but not retrograde ejaculation, acting through peripheral actions on the seminal vesicle, vas deferens and prostate.[13,18] Hisasue *et al.* provided histopathological confirmation that α1A-adrenoreceptor is expressed predominantly in human seminal vesicles.[18] Suppression of seminal emission might lead to prolonged ejaculation latency. Nagai *et al.* used color Doppler to show that ejaculation begins with seminal emission to the prostatic urethra.[19] Silodosin inhibits this first step of ejaculation. Therefore, we speculate that silodosin prolongs IELT by suppressing seminal emission as the trigger of ejaculation.

Potential problems of silodosin treatment are anejaculation, decreased semen volume and some discomfort with orgasm.[11,12,14] In the present study, 25% of the patients experienced anejaculation; 37.5% experienced reduced semen volume; and 87.5% experienced discomfort during orgasm. These symptoms might impair QOL in the general population. However, these problems were not significant for the participants in the present study. We speculate that the longer sexual intercourse time might compensate for these adverse symptoms in PE patients, although further QOL studies are required. In addition, we informed patients of reduced semen volume or anejaculation as possible adverse events before starting treatment. Therefore, the patients could prepare for these adverse events.

One of the potential benefits of silodosin is its safety. There were no systemic adverse events in the present study. When treating LUTS, the incidence of orthostatic hypotension was low. Long-term safety was also confirmed in previous studies, even in elderly people.[10] Because silodosin has greater affinity for the α1A-adrenoreceptor than for the α1B-adrenoreceptor, it minimizes the propensity for blood pressure-related adverse effects caused by α-1B-adrenoreceptor blockade.[9,10] This evidence suggests that the safety of silodosin treatment for PE equals that of off-label SSRI and dapoxetine. Potential treatment-related adverse effects of SSRI and dapoxetine are nausea, diarrhea, headache, fatigue, yawing and dizziness. Serious complications of SSRI include an increased risk of suicidal ideation and suicide attempts, and withdrawal symptoms with abrupt SSRI cessation are known in patients with major psychiatric disorders;[20] however, these safety risks have not been previously evaluated in men with PE.[6]

There were some limitations in the present study, such as lack of a control study and evaluation for general QOL. There is room for improvement in the form of more accurate measurement of IELT. The authors are going to plan a placebo controlled randomized study with evaluation of the clinical usefulness of silodosin, and evaluation of patients' and partners' general QOL.

The present preliminary study suggests the possible use of silodosin as a new treatment option for PE. We hope that this report will facilitate further studies to develop and evaluate the indications for and safety of silodosin for PE.

Conflict of interest

None declared.

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