Up-titration of vardenafil dose from 10 mg to 20 mg improved erectile function in men with spinal cord injury

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Aim: Vardenafil is a highly selective phosphodiesterase type-5 inhibitor for the treatment of erectile dysfunction (ED). Efficacy of vardenafil has been demonstrated in various ED populations, but that in Japanese patients with spinal cord injury (SCI) has not been assessed.

Methods: This was an open-label, multicenter, flexible dose, 12-week study in patients with ED due to SCI. Following a 4-week observation period, patients received vardenafil 10 mg for 4 weeks, and based on efficacy, tolerability and patient preference, doses for the remaining 8 weeks were decided by investigators. The primary efficacy parameter was erectile function domain score of the International Index of Erectile Function.

Results: Ten patients took 10 mg all through the study, while 22 patients took 20 mg after completing 4 weeks’ treatment with 10 mg. The erectile function domain score increased from 12.2 at baseline to 25.0 at Last Observation Carried Forward (LOCF) in the former group and from 10.3 to 22.5 in the latter group, respectively. Importantly, there was a 5.0 point increase in erectile function domain score after up-titration in the latter group. Drug-related adverse events were observed in 22% of patients including hot flushes (9%) and headache (6%), but these were transient and mild in intensity. Serious adverse events and adverse events leading to discontinuation of the study drug were not reported.

Conclusions: Vardenafil 10 and 20 mg was well tolerated and improved erectile function in patients with SCI. Of interest, erectile function was further improved by 20 mg in patients who were not sufficiently treated with 10 mg.

Key words erectile dysfunction, Japan, phosphodiesterase type 5 inhibitor, spinal cord injury, vardenafil.

Introduction

Erectile dysfunction (ED), the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual activity,1 is a common complication of spinal cord injury (SCI). Despite the fact that many men with SCI are capable of having some degree of erectile response, it is often not hard enough or does not last long enough for sexual activity.2 Hence, more than 80% of patients with SCI have ED in the USA,3 while up to 71% of patients with SCI have ED in the UK.4,5 The number of patients with SCI in Japan is reported to be more than 100 000, with 5000 new cases reported per year.6 As 80% of them are male, many patients with SCI (4800–36 000) are considered to have ED in Japan as well.7

Since the introduction of the first phosphodiesterase type-5 (PDE5) inhibitor, sildenafil, effective oral treatment for ED has been available since 1998 in the USA and 1999 in Japan. However, the effective ED treatments in difficult-to-treat patients have been restricted in Japan, where high-dose PDE5 inhibitors or intracavernosal injection of prostaglandin E1 have not received regulatory approval. This means that many ED patients in Japan with SCI are considered to be insufficiently treated.

Vardenafil, a new PDE5 inhibitor, is more selective for PDE5 and more biochemically potent than sildenafil by in vitro and in vivo studies when tested under the same conditions.8–11 Clinical efficacy of vardenafil has also been demonstrated in various ED patient populations, including patients with diabetes,12 patients post-radical prostatectomy,13 and in patients non-responsive to sildenafil by history.14 These properties suggest that vardenafil may be a highly efficacious oral treatment in difficult-to-treat ED patients, such as those with SCI.

Giuliano et al. reported that a flexible dose of vardenafil (5–20 mg) improved key efficacy parameters of erectile function irrespective of ED severity in patients with ED due to traumatic SCI.15 Hence, in this study, the efficacy, tolerability, and safety of vardenafil 10 and 20 mg were assessed in Japanese ED patients with SCI, particularly whether high-dose vardenafil (20 mg) could demonstrate dose-dependent improvement over 10 mg in this patient population.
Methods

Patients

Thirty-eight patients were enrolled in this trial between March and November 2004. At the first visit, patients were registered for participation in the trial and were provided with written informed consent. They entered a 4-week unmedicated observation period in which they could not use any PDE5 inhibitors, or any other therapies for ED. Patients not in accordance with inclusion and exclusion criteria were withdrawn at this stage.

Inclusion criteria

Inclusion criteria were as follows: (i) Men with erectile dysfunction according to the NIH Consensus Statement (inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance), solely as a result of a traumatic injury to the spinal cord (suffered SCI more than 6 months ago); (ii) Patient answers ‘yes’ to the question regarding the presence of residual erectile function over the past 6 months [At home over the past 6 months, have you experienced at least some enlargement of your penis in response to: (i) mechanical stimulation by yourself or your partner; or (ii) visual stimulation?] (iii) Age between 20 and 64 years old; (iv) Heterosexual relationship; (v) Patient must make at least four attempts at sexual intercourse (according to the question in the patient diary: ‘Was sexual activity initiated with the intention of intercourse?’) on four separate days during the untreated baseline period, and at least 50% of the attempts during this period must have been unsuccessful, according to the following questions from the patient diary [at least one question should be answered with ‘No’]: ‘Were you able to achieve at least some erection (some enlargement of penis)?’, ‘Were you able to insert your penis into your partner’s vagina?’, and ‘Did your erection last long enough for you to have successful intercourse?’; and (vi) Documented, written informed consent.

Exclusion criteria

Exclusion criteria were as follows: (1) Any unstable medical, psychiatric or substance abuse disorder that in the opinion of the investigator would significantly impair erectile function; (11) Unstable angina pectoris; (12) History of myocardial infarction, stroke or life-threatening arrhythmia within the prior 6 months; (13) Congenital QT prolongation (long QT syndrome); (14) Uncontrolled atrial fibrillation/flutter at screening (ventricular response rate ≥100 bpm); (15) NYHA Class III and IV heart failure; (16) Clinically significant hematological disease which may lead to priapism such as sickle cell anemia, multiple myeloma and leukemia; (17) Bleeding disorder; (18) Significant active peptic ulceration; (19) Resting hypotension (a resting systolic blood pressure of <90 mmHg) or hypertension (a resting systolic blood pressure >170 mmHg or a resting diastolic blood pressure >110 mmHg); (20) Symptomatic postural hypotension within 6 months of the 1st visit; (21) History of malignancy within the past 5 years (other than squamous or basal cell skin cancer); (22) Severe chronic or acute liver disease, history of moderate or severe hepatic impairment; (23) Patients who are taking nitrates or nitric oxide donors; (24) Patients who are taking the following potent inhibitors of cytochrome P-450 3A4: HIV protease inhibitors such as ritonavir or indinavir, the antimycotic agentsitraconazole and ketoconazole (topical forms are allowed) or erythromycin; (25) Patients who are taking anticoagulants, except for antiplatelet agents; (26) Patients who are taking antian-drogens, androgens (e.g. testosterone), or trazodone; (27) Patients who are taking alpha-blocker or carperitide; (28) Patients who are taking an antiarrhythmic agent of Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol); (29) Patients who have received any study drug (including placebo) within 30 days of the first visit; (30) Use of any treatment for ED within 7 days of the first visit or during the study, including oral medications, vacuum devices, constrictive devices, injections or urethral suppositories; (31) Patients with fasting blood glucose ≥126 mg/dL or random blood glucose ≥200 mg/dL, and with HbA1c ≥6.5% at the first visit; (32) Patients who have a serum total testosterone level <75% of the lower limit of normal according to the range of the testing laboratory at the first visit. However, patients whose initial values are evaluated to have been low just due to the timing of blood sampling can undergo re-examination one more time; (33) Patients with a serum creatinine >3.0 mg/dL at the first visit; (34) Elevation of AST (GOT) and/or ALT (GPT) > three times the upper limit of normal at the first visit; (35) Patients unwilling to cease use of vacuum devices, intracavernos injection, sildenafil or other therapies for ED; (36) Known hypersensitivity to vardenafil or any component of the investigational medication; (37) Patients who have experienced no enlargement of penis with the use of a PDE5 inhibitor and/or who have previously discontinued PDE5 inhibitor therapy due to an adverse drug reaction (ADR); (38) Primary hypoactive sexual desire; (39) Patients who are illiterate or unable to understand the questionnaires or patient diary; (40) Patients who are unwilling or unable to complete the questionnaires or the patient diary; (41) Patients judged as inappropriate for enrollment: (e.g. from the results of centralized electrocardiogram [ECG] reading).
Study design
This was an open-label study to investigate the efficacy and safety of 10 and 20 mg vardenafil in SCI patients with ED. Following 4 weeks’ observation period, patients were entered into 12 weeks’ treatment phase. They were instructed to take one tablet of vardenafil 10 mg about 1 h before sexual intercourse. Dosing was restricted to one tablet per day (24 h). Patients were given the option to titrate from 10 to 20 mg after 4 weeks of treatment and continue on 20 mg for the remainder of the treatment phase, if it was judged by the investigator that their response on 10 mg was inadequate and that they would be able to tolerate the 20 mg dose.

Efficacy parameters
The intent-to-treat (ITT) population (patients who took at least one dose of study medication and for whom baseline and any post-baseline efficacy data are available) was used for the analysis. The primary predefined outcome variable was the 12-week Last Observation Carried Forward (LOCF) score of International Index of Erectile Function (IIEF) erectile function (EF) domain score (the sum of Questions 1–5 plus Question 15).16

The following variables were also evaluated in this study: per patient success rate on the patient’s diary concerning ‘Success in penetration’ (SEP2), ‘Success in maintaining erection during intercourse’ (SEP3) during visits, and other IIEF domain scores (intercourse satisfaction, overall satisfaction, orgasmic function and sexual desire) at week 4, 8 and 12 (as observed and LOCF).

Safety parameters
The safety population (patients who took at least one dose of study medication and for whom any post-baseline safety data are available) was the same as the ITT population. Safety was evaluated by recording of adverse events and from physical examination, vital sign determination (including 12-lead ECG), and standard laboratory tests.

Observations
Patients were requested to complete diary entries at the time of each dose and met with the investigator every 4 weeks during the study to assess the IIEF questionnaires, other efficacy parameters and adverse events. At the first visit (registration), and at the last visit (week 12) or at the time of premature withdrawal, heart rate, blood pressure, 12-lead ECG and laboratory tests were performed. Laboratory tests were also performed at second visit (week 0), third visit (week 4) and additionally at fourth visit (week 8), if dose was titrated up to 20 mg at week 4.

Statistics
No formal sample size estimation was made.

For each dosing group, the EF domain score at week 12 (LOCF) was summarized using the mean and standard deviation, median, quartiles, and minimum/maximum. The 95% confidence interval (CI) of the change from baseline was also presented with associated descriptive statistics.

Ethics
The protocol of this clinical trial was approved by the appropriate Institutional Review Boards. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol was complied with the requirements specified in Item 3 of Article 14 and Item 2 of Article 80 in the Pharmaceutical Affairs Law in Japan, and the Good Clinical Practice (GCP) issued on April 1, 1997.

Results
Patients
A total of 38 patients were enrolled into this study. Efficacy and safety of vardenafil was evaluated in 32 patients who met inclusion/exclusion criteria. Of the 32 patients, 10 patients continued 10 mg throughout the study (10/10 mg group) and 22 patients were titrated up to 20 mg after 4 weeks’ treatment on 10 mg (10/20 mg group). A total of 31 patients completed the 12 weeks’ treatment phase and one patient withdrew before 12 weeks. The reason for premature termination was withdrawal of consent to participate in ‘Paralympic’.

The baseline characteristics for the two treatment groups (i.e. 10/10 and 10/20) were similar in terms of age, body mass index, and duration of ED (Table 1). However, the baseline IIEF EF domain score in the 10/20 mg group (10.3) was slightly lower than that in the 10/10 mg group (12.2).

Efficacy
Primary efficacy parameters
The IIEF EF domain score improved from 12.2 at baseline to 25.0 at week 12 (LOCF) in the 10/10 mg group. In these patients, EF domain scores were improved to 26.9 (normal range) at week 4, and maintained thereafter. The improvement was clinically meaningful on the IIEF.17

The IIEF EF domain score improved from 10.3 at baseline to 22.5 at week 12 (LOCF) in the 10/20 mg group. Analysis of EF domain scores by visit demonstrated incremental improvement after titration up to 20 mg from 10 mg in the this group: 17.5 at week 4 and 22.3 at week 8 (Fig. 1). This was also a clinically meaningful improvement.

Secondary efficacy parameters
Mean success rates to the questions in Patient Diary by visit also supported incremental efficacy of 20 mg after up-titration. Patients in the 10/20 mg group answered ‘Yes’ to the question, ‘Success in penetration’ at week 4 after treatment with vardenafil 10 mg for 56% of attempts. The ‘Yes’ answer to this question further increased after up-titration to 20 mg (76% at week 8, 83% at week 12) (Fig. 2). Furthermore, patients in the 10/20 mg group answered ‘Yes’ to the question, ‘Success in maintaining erection during intercourse’ at week 4 for 43% of attempts. The ‘Yes’ answer to this question further increased after up-titration to 20 mg (62% at week 8, 69% at week 12) (Fig. 3). In

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contrast, patients in the 10/10 mg group answered ‘Yes’ to the question, ‘Success in penetration’ and ‘Success in maintaining erection during intercourse’ at week 4 for 88% and 81% of attempts, respectively, and the success rates were maintained throughout the study period.

**Safety**

Drug-related adverse events were observed in seven (22%) patients. The most common events were hot flush (9%) and headache (6%), which were mild in intensity and transient, and are commonly reported with PDE5 inhibitors. There were no serious adverse events and no adverse events which led to the premature discontinuation in this study (Table 2). Concerning new drug-related adverse events after titration to 20 mg, only mild palpitations were reported in one patient. Vardenafil was safe and generally well tolerated in this study.

**Discussion**

The introduction of PDE5 inhibitors has provided many ED patients with the chance to overcome their erectile dysfunction.
difficulties. However, treatment options for difficult-to-treat ED patients, such as patients with traumatic SCI, are limited in Japan, where high-dose PDE5 inhibitors or intracavernosal injection/intraurethral injection of prostaglandin E1 are not approved. Considering these points, current treatment options in Japan are not sufficient for these patients. Therefore, it is important to evaluate whether high-dose PDE5 inhibitors can offer a chance for difficult-to-treat ED patients, such as those with SCI, to improve their erectile function. This study was planned, for the first time in Japan, to assess efficacy and safety of vardenafil 10 and 20 mg in a SCI population.

First, the result clearly demonstrated incremental efficacy of vardenafil 20 mg in patients who were insufficiently treated with 10 mg. Twenty-two (69%) patients titrated up to 20 mg after week 4 (forming the 10/20 mg group), and these patients had worse erectile function at baseline (EF domain score = 10.3) than those who took 10 mg throughout the study (10/10 mg group). However, the improvement of erectile function in patients in the 10/20 mg group was dramatic following vardenafil treatment, and IIEF EF domain score was further increased by 5 points after up-titration to 20 mg (Fig. 1). The result was robust as secondary efficacy parameters, such as SEP2 (Fig. 2) and SEP3 (Fig. 3), also consistently supported incremental efficacy of vardenafil 20 mg to 10 mg.

Compared to erectile function at week 4 (after 4 weeks’ treatment with vardenafil 10 mg), patients have additionally become able to successfully insert their penis into their partner’s vagina (56% at week 4, 83% at LOCF), or able to maintain erections long enough to successfully complete intercourse (43% at week 4, 69% at LOCF) by more than 25% of attempts, after up-titration to 20 mg, although this is the result of small number of patients (n = 22). The most common adverse events were hot flush (9%) and headache (6%), which are consistent with the adverse event profile of PDE5 inhibitors.12,18–20 All of these events were mild in intensity and transient. Vardenafil was safe and generally well tolerated in this study.

It had been considered that ED due to SCI is not so difficult-to-treat because SCI patients are typically younger men with no organic damage to the cavernosal tissue and because these patients have intact sexual function before injury, which is different from other ED populations such as those with diabetes accompanying complications of vascular disease and neuropathies.21 However, the present results indicate that many Japanese ED patients with SCI also require high-dose PDE5 inhibitors, and that their erectile function was further improved by titration up to 20 mg.

The present results are comparable to those of other reports, in which vardenafil has been shown to improve erectile function in patients with ED due to SCI.15 Patients treated with a flexible dose of vardenafil (5–20 mg) were able to successfully insert their penis into their partner’s vagina for 76% of attempts, compared to 41% of those taking placebo, and they were able to maintain erections long enough to successfully complete intercourse for 59% of attempts, compared to 22% of those taking placebo.

With continuing advances in medical technologies and subsequent decreases in mortality rates due to traumatic SCI, quality of life has now become a major concern for these patients.21 This study demonstrated for the first time in Japanese SCI patients that incremental efficacy of vardenafil 20 mg can be expected in patients who are insufficiently treated with currently recommended doses of PDE5 inhibitors, without increasing risk on safety profile.

In conclusion, vardenafil 10 and 20 mg are effective to treat ED in SCI patients, and more importantly, 20 mg showed a significant dose-dependent improvement over the 10 mg dose in this patient population. Vardenafil was safe and generally well tolerated in this study.

### Table 2 Drug-related adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Vardenafil (10/10 mg group) (n = 10)</th>
<th>Vardenafil (10/20 mg group) (n = 22)</th>
<th>Total (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>4 (40%)</td>
<td>3 (14%)</td>
<td>7 (22%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>3 (30%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0%)</td>
<td>2 (9%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

**Fig. 3** Percentage of patients answering ‘Yes’ to the SEP3 diary question, ‘Did your erection last long enough for you to have successful intercourse?’ for 10 mg/10 mg and 10 mg/20 mg groups at weeks 0, 4, 8 and 12, and at last observation carried forward (LOCF).
Acknowledgment

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References