Asian Journal of Andrology (2014) 16, 725–727

www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Sexual Function

Comparison of paroxetine and dapoxetine, a novel selective serotonin reuptake inhibitor in the treatment of premature ejaculation

Abdulmuttalip Simsek[1], Sinan Levent Kirecci[2], Onur Kucuktopcu[1], Faruk Ozgor[1], Mehmet Fatih Akbulut[1], Omer Sarilar[1], Unsal Ozkuvanci[1], Zafer Gokhan Gurbuz[1]

Dapoxetine hydrochloride is a selective serotonin reuptake inhibitor and the first drug approved for the on-demand treatment of premature ejaculation (PE). Our objective in this study was to characterize the efficacy of on-demand dapoxetine (30 and 60 mg) and daily paroxetine (20 mg) usage in treating PE. We conducted a 1 month study involving a total of 150 patients. Patients were divided into three groups of 50. Group 1 were treated with on-demand dapoxetine (30 mg), Group 2 with on-demand dapoxetine (60 mg) and Group 3 with daily paroxetine (20 mg). Our outcome measurement was increased from baseline intravaginal ejaculatory latency time (IELT) after treatment. The IELT increased from baseline to posttreatment by 117%, 117% and 170% in the paroxetine group ($P < 0.01$), 30 mg dapoxetine group ($P < 0.01$) and 60 mg dapoxetine group ($P < 0.01$), respectively. The increase from baseline IELT were similar for the 30 mg dapoxetine and paroxetine groups ($P > 0.05$), while the 60 mg dapoxetine group had a larger posttreatment IELT increase compared with the 30 mg dapoxetine ($P < 0.05$) and paroxetine ($P < 0.01$) groups. Dapoxetine (60 mg) 1–3 h before planned intercourse is a very effective treatment modality for PE. However, an on-demand dose of 30 mg dapoxetine is no more effective than the currently prescribed paroxetine treatment.

Asian Journal of Andrology (2014) **16**, 725–727; doi: 10.4103/1008-682X.128467; published online: 09 May 2014

Keywords: dapoxetine; paroxetine; premature ejaculation; selective serotonin reuptake inhibitor

INTRODUCTION

International Society for Sexual Medicine defines premature ejaculation (PE) as a "male sexual dysfunction characterized by ejaculation which is always or nearly always occurs prior to or within 1 min of vaginal penetration; and an inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy."[1] With a general prevalence rate of between 20% and 40%, PE is the most common sexual dysfunction in men.[2–4]

The intravaginal ejaculatory latency time (IELT) is defined as the time from vaginal intromission to intravaginal ejaculation.[5] In practice the IELT is often used as a method of quantifying the response to treatment and as a standardized method of comparing treatments within clinical trials.

Until recently PE was treated by behavioral techniques such as the squeeze technique[6] and stop–start method.[7] Prior to the use of dapoxetine, there were no approved pharmacological therapies for PE; therefore, treatment involved the off-label use of selective serotonin reuptake inhibitors (SSRIs) and topical agents, alone and in combination with other drugs.[8–12]

Dapoxetine (Priligy™ Johnson and Johnson, NJ, USA) is a novel SSRI, which acts by potent inhibition of 5-HT transport. As a short acting SSRI, dapoxetine is probably better suited to use as an on-demand treatment for PE.[13–15] Few studies have compared the performance of paroxetine and dapoxetine in the treatment of PE. Here, we have prospectively compared the safety and efficacy of daily paroxetine and dapoxetine (30 and 60 mg doses) in patients with PE.

MATERIALS AND METHODS

We evaluated 150 patients (between 30 and 36-year-old) suffering from PE and referred to our outpatient clinic between October 2011 and May 2013. All patients were married potent men in a stable relationship for at least 6 months and had an uncontrolled ejaculation within 1 min of vaginal intromission, with no obvious organic cause for PE. Study exclusion criteria were: erectile dysfunction; low libido; major psychiatric or psychological illness including depression; alcohol, drugs or substances abuse; organic diseases (hypothyroidism or hyperthyroidism, asthma, cardiac arrhythmias, diabetes mellitus) causing limitation in using SSRIs; and use of other treatments for PE within the previous 3 months. A detailed history, including a medical and sexual history, was recorded and a complete physical examination performed. Patients did not have a psychological consultation and female partner satisfaction was not assessed during or after the study. Patients completed the International Index of Erectile Function questionnaire and IELT recorded before and after drug administration. IELT was determined by stopwatch method for every intercourse attempt.

[1]Department of Urology, Haseki Research and Training Hospital, Fatih, Istanbul, [2]Department of Urology, Sisli Etfal Research and Training Hospital, Istanbul, Turkey.
Correspondence: Dr. A Simsek (simsek76@yahoo.com)
Received: 26 October 2013; Revised: 18 November 2013; Accepted: 20 February 2014

Patients were divided into three equal groups of 50 patients. Group 1 patients received 30 mg dapoxetine 1–3 h before planned intercourse. Group 2 patients received 60 mg dapoxetine 1–3 h before planned intercourse and Group 3 patients received 20 mg paroxetine once a day for a month. All patients followed-up for 1 month, beginning after initiation of treatment.

Statistical analysis

Results of all groups are shown as mean ± standard deviation. Statistical analyses of the IELT were calculated by the Analysis of variance, Tukey's test and Paired *t*-test using SPSS version 13 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was accepted as a statistically significant value. Minimum sample size was estimated using an a priori power analysis based on a confidence level of 0.95 and a power of 0.80. Mean of the IELT differences was based on first 10 patients' data.

RESULTS

Patients' demographic data are given in **Table 1**. The average age of all the patients was 33.1 ± 3.2 year and the mean baseline IELT was 44.9 ± 25.1 s. There was no difference between groups in terms of age ($P = 0.18$), body mass index ($P = 0.13$), duration of marriage ($P = 0.20$) or baseline IELT ($P = 0.87$).

The IELT increase from baseline to posttreatment was 117% in the 30 mg dapoxetine group ($P < 0.01$), 170% in the 60 mg dapoxetine group ($P < 0.01$), and 117% in the paroxetine group ($P < 0.01$). The improvement of baseline IELT were similar for the 30 mg dapoxetine and paroxetine groups ($P > 0.05$), whereas the improvement of IELT of 60 mg dapoxetine group was better than both the 30 mg dapoxetine ($P < 0.05$) and paroxetine group ($P < 0.01$) (**Table 2**).

All treatments were well-tolerated by all patients. The most adverse effects associated with daily paroksetine administration were yawning, akathisia and somnolance. Less adverse effects associated with dapoxetine were yawning, nausea, dizziness, and headache (30 and 60 mg doses) (**Figure 1**). Seven patients in paroksetine group dropped out for side effects (mood related changes, somnolance) and 10 patients in dapoxetine group dropped out at the end of the month (two of effect below expectations, five of costs and three of side effectsnausea, and headache).

DISCUSSION

Although nonlethal, PE can severely negatively affect quality-of-life. Despite the high prevalence of this condition, there is little research regarding its causation and it is likely that there are both biological and psychological factors. Penile hypersensitivity, hyper excitable ejaculatory reflex, increased sexual arousability, endocrinological problems, genetic predisposition and serotoninergic receptor dysfunction have been proposed as biological factors.[8] PE psychological risk factors include social phobia, anxiety, relationship problems, infrequent sexual intercourse, and lack of sexual experience.[9]

Although PE has been historically treated with alpha adrenergic blocking agents and monoamine oxidase inhibitors, side-effects limited the use of these treatments. More recently, newly developed drugs such as antidepressants, local anesthetic agents and phosphodiesterase type 5 inhibitors have been applied as PR treatments.

The delaying effect of SSRIs on ejaculation was first described by Patterson when treating men with depression.[16] The SSRI's block 5-HT transporter mechanisms and so increase 5-HT within the synapses.[9] At least three serotonin receptor subtypes have been identified as having a role in ejaculation, including 5-HT1a, 5-HT1b and 5-HT2c.[13] Activation of 5-HT2c receptors delays ejaculation; however, the extent of this delay depends on several factors including the type, dose and frequency of drug administration, as well as the genetically determined ejaculatory threshold set point.[17]

Waldinger *et al*.[18] enrolled the first randomized controlled trial assessing the use of paroxetine in PE treatment. and found that paroxetine has substantially greater efficacy than sertraline and fluoxetine.[19] Neither paroxetine, sertraline or fluoxetine are registered drugs approved for PE. Dapoxetine is currently the only drug approved (in limited numbers of countries) for use as a PE treatment. Results from placebo-controlled, randomized, multicenter phase III trials have demonstrated that men with PE receiving dapoxetine (30 or 60 mg) experienced increased IELT and higher levels of control over ejaculation and satisfaction with sexual intercourse.[20]

Dapoxetine is a novel SSRI that is stereochemically similar to many other described SSRIs.[13] Pharmacological studies have shown dapoxetine to be a potent inhibitor of the 5-HT transporter[14] and that its pharmacokinetics are unaffected by age, ethnicity or dosing frequency (for 30 and 60 mg doses). Dapoxetine demonstrates rapid absorption and elimination with minimal accumulation following daily dosing, and is extensively metabolized by multiple enzymes.[15,21] As a short acting SSRI dapoxetine is probably better suited as an on-demand treatment for PE. Doses of 30 and 60 mg have been used and peak

Table 1: Demographic data (mean±s.d.) in premature ejaculation patients who received dapoxetine and paroxetine

	Dapoxetine 30 mg	*Dapoxetine 60 mg*	*Paroxetine 20 mg*	*P*
Number of patient	50	50	50	
Age (year)	33.50±3.45	32.40±2.90	33.49±3.50	0.18
BMI (kg m^{-2})	23.40±4.94	23.30±6.52	22.94±4.21	0.13
Duration of marriage (year)	6.70±5.76	4.80±4.80	5.12±3.30	0.20

SD: standard deviation; BMI: body mass index

Table 2: IELT (mean±s.d.) before and after treatment with dapoxetine and paroxetine in premature ejaculation patients

	Dapoxetine 30 mg			*Dapoxetine 60 mg*			*Paroxetine 20 mg*		
	Before	*After*[a]	*P*	*Before*	*After*[b]	*P*	*Before*	*After*[c]	*P*
IELT	46.1± 23.2	100.2± 24.5	0.001	43.5± 20.6	118.2± 40.8	0.001	45.2± 31.6	98.4± 26.3	0.001

IELT: intravaginal ejaculatory latency time; SD: standard deviation. No statistical difference among groups concerning baseline IELT (P=0.87). [a versus b]P<0.05; [a versus c]P>0.05; [b versus c]P<0.01

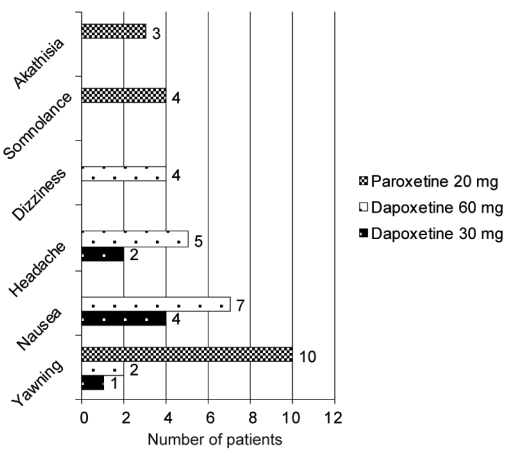

Figure 1: Adverse effects of all groups.

plasma concentrations observed 1.01 and 1.27 h after administration. Elimination is also rapid, with a half-life of 1.3–1.4 h.[15,22]

Dapoxetine is contraindicated in men with moderate to severe hepatic impairment and in those receiving concomitant therapy with potent cytochrome P450 3A4 inhibitors (e.g., ketoconazole, ritonavir, and telithromycin), thioridazine, monoamine oxidase inhibitors, serotonin reuptake inhibitors (e.g., SSRIs, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants) or other medicinal/herbal products with serotonergic effects (e.g., hypericum [St John's wort]). Dapoxetine is not recommended in men with severe renal impairment, and caution is advised in men with mild to moderate renal impairment. Alcohol and recreational drugs should be avoided when taking dapoxetine.

In our study, seven patients (14%) in paroksetine group dropped out for side effects (mood related changes and somnolence) and these side effects appeared in the 1st week. 10 patients (10%) in dapoxetine group dropped out at the end of the month (two of them effect below expectations, five of them costs and three of side effectsnausea, and headache). In contrast, discontinuation rates were higher than in the literature. Mondaini reported that 26% dropped out after 1 month dapoxetine treatment.[23] Although it seems like discrepancy we believe that these differences may be related to patient's demographic diversity.

In several studies dapoxetine has been shown to significantly improve the IELT compared with baseline and placebo levels; IELT 1.66, 3.03 and 3.15 min with placebo, 30 mg dapoxetine and 60 mg respectively, when the drug was taken 30–60 min before intercourse. When taken 3 h–4 h prior to intercourse the IELT was 1.79, 3.06 and 3.97 min with placebo, for 30 and 60 mg dapoxetine respectively.[24]

In contrast to our study, Safarinejad found paroxetine to be more effective in terms of satisfaction and IELT. Safarinejad's study divided 340 potent male patients into paroxetine (20 mg) and dapoxetine (60 mg) groups. Intercourse satisfaction and IELT increment was higher in the paroxetine group.[25]

In present study, all three groups tolerated the drugs well and no drug withdrawal was seen. Although adverse effects such as yawning and somnolence, asthenia, nausea and headache were reported by some patients, in our opinion dapoxetine has a lower adverse effect profile.

Some limitations in our study include a low patient number, lack long-term follow-up and short follow-up period. In addition, our study did not compare female partner and male intercourse satisfactions or perceived improvement in control over ejaculation of male.

Few studies have made direct comparison between paroxetine and dapoxetine. To the best of our knowledge, our study is the first to compare the performance of paroxetine in PE patients at 30 and 60 mg doses. A large populated, multicenter, double-blind and placebo controlled prospective randomized study is needed to evaluate the efficacy of dapoxetine over paroxetine.

CONCLUSION

On demand dapoxetine is a novel effective treatment modality for PE. Although a lower dose of dapoxetine (30 mg) does not outperform the currently used paroxetine treatment, 60 mg dapoxetine 1–3 h before planned intercourse produces a greater increase in IELT for men with PE, compared to paroxetine. We propose that in cases of severe PE (e.g., IELT <30 s), 60 mg dapoxetine should be given directly.

AUTHOR CONTRIBUTIONS

AS carried out the studies and drafted the manuscript and performed the statistical analysis. SLK, OS, ZGG, FO, MFA, UO and OK designed the study and reviewed the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

REFERENCES

1 McMahon CG, Althof S, Waldinger MD, Porst H, Dean J, *et al*. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *BJU Int* 2008; 102: 338–50.
2 Althof SE. Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *J Urol* 2006; 175: 842–8.
3 Carson C, Gunn K. Premature ejaculation: definition and prevalence. *Int J Impot Res* 2006; 18 Suppl 1: S5–13.
4 Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, *et al*. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol* 2007; 51: 816–23.
5 Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, *et al*. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med* 2005; 2: 492–7.
6 Masters WH, Johnson VE. Premature ejaculation. In: masters WH, Johnson VE, editors. Human Sexual Inadequacy. Boston MA: little, Brown and Company; 1970. p. 92-115.
7 Semans JH. Premature ejaculation: a new approach. *South Med J* 1956; 49: 353–8.
8 McMahon C. Premature ejaculation: past, present, and future perspectives. *J Sex Med* 2005; 2 Suppl 2: 94–5.
9 Wylie KR, Ralph D. Premature ejaculation: the current literature. *Curr Opin Urol* 2005; 15: 393–8.
10 Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, *et al*. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol* 2010; 57: 804–14.
11 Jannini EA, Porst H. Case studies. A practical approach to premature ejaculation. *J Sex Med* 2011; 8 Suppl 4: 360–7.
12 Henry R, Morales A, Wyllie MG. TEMPE: topical eutectic-like mixture for premature ejaculation. *Expert Opin Drug Deliv* 2008; 5: 251–61.
13 Hellstrom WJ. Emerging treatments for premature ejaculation: focus on dapoxetine. *Neuropsychiatr Dis Treat* 2009; 5: 37–46.
14 Andersson KE, Mulhall JP, Wyllie MG. Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. *BJU Int* 2006; 97: 311–5.
15 Modi NB, Dresser MJ, Simon M, Lin D, Desai D, *et al*. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006; 46: 301–9.
16 Patterson WM. Fluoxetine-induced sexual dysfunction. *J Clin Psychiatry* 1993; 54: 71.
17 Sadeghi-Nejad H, Watson R. Premature ejaculation: current medical treatment and new directions (CME). *J Sex Med* 2008; 5: 1037–50.
18 Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994; 151: 1377–9.
19 Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res* 2004; 16: 369–81.
20 Pryor JL, Althof SE, Steidle C, Miloslavsky M, Kell S. Efficacy and tolerability of dapoxetine in the treatment of premature ejaculation. *J Urol* 2005; 173: 201.
21 Dresser MJ, Kang D, Staehr P, Gidwani S, Guo C, *et al*. Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. *J Clin Pharmacol* 2006; 46: 1023–9.
22 Thyssen A, Sharma O, Tianmei S, Aquilina JW, Vandebosch A, *et al*. Pharmacokinetics of dapoxetine hydrochloride in healthy Chinese, Japanese, and Caucasian men. *J Clin Pharmacol* 2010; 50: 1450–60.
23 Mondaini N, Fusco F, Cai T, Benemei S, Mirone V, *et al*. Dapoxetine treatment in patients with lifelong premature ejaculation: the reasons of a "Waterloo". *Urology* 2013; 82: 620–4.
24 Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, *et al*. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006; 368: 929–37.
25 Safarinejad MR. Comparison of dapoxetine versus paroxetine in patients with premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. *Clin Neuropharmacol* 2006; 29: 243–52.

How to cite this article: Simsek A, Kirecci SL, Kucuktopcu O, Ozgor F, Akbulut MF, Sarilar O, Ozkuvanci U, Gurbuz ZG. Comparison of paroxetine and dapoxetine, a novel selective serotonin reuptake inhibitor in the treatment of premature ejaculation. *Asian J Androl* 09 May 2014. doi: 10.4103/1008-682X.128467. [Epub ahead of print]