Tramadol HCL has Promise in On-Demand Use to Treat Premature Ejaculation

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ABSTRACT

Introduction. Premature ejaculation (PE) is a worldwide problem without an approved treatment. Selective serotonin reuptake inhibitors (SSRIs) are widely used “off label” as pharmacotherapeutic agents in the treatment of PE. Aim. This study investigates Tramadol efficacy for on-demand treatment of PE. Main Outcomes Measures. Intravaginal ejaculation latency time (IELT) was used as an objective tool to assess the efficacy of the investigated treatments. Materials and Methods. Single-blind, placebo-controlled, crossover, stopwatch monitored two-period study was conducted, on 60 patients with lifelong PE. PE was defined as IELT of <2 minutes in 80% of intercourse episodes. A total of 25 mg of Tramadol hydrochloride was given to one group (30) prior to intercourse and placebo was supplied for the other group (30) for 8 weeks. Drugs were taken 1–2 hours before sexual activity and sexual intercourse was required at least once per week. After the initial treatment period, the two groups took the alternate medication for another 2 months. The two 8-week treatment periods were separated by 1 week washout period. IELT was timed by a stopwatch at each intercourse and was reported by patients or partners. Results. The baseline (mean ± SD) IELT for patients before treatment was 1.17 ± 0.39 minutes. At the end of the treatment period utilizing the active drug, the mean IELT was increased significantly in patients on Tramadol treatment to 7.37 ± 2.53 minutes. The same patients on placebo medication had mean IELT of only 2.01 ± 0.71 minutes. Patients uniformly reported satisfaction with their resulting control over ejaculation. Conclusions. Tramadol, a drug with a proven safety record as an anti-inflammatory agent, shows promise as a drug for treating rapid ejaculation. Salem EA, Wilson SK, Bissada NK, Delk JR II, Hellstrom WJ, and Cleves MA. Tramadol HCL has promise in on-demand use to treat premature ejaculation. J Sex Med 2008;5:188–193.

Key Words. Design; Methodology of Clinical Trials; Causes and Treatment of Ejaculatory/Orgasmic Disorders; Premature Ejaculation

Introduction

Premature ejaculation (PE) is the most common male sexual disorder, and is estimated to affect up to 30% of men worldwide [1]. Although the etiology is unclear, there is emerging evidence that men from different ethnic backgrounds may be more at risk [2]. PE, unlike erectile dysfunction (ED), affects men of all ages equally. However, both PE and ED coexist, and often PE can masquerade or be misdiagnosed as ED in many men. This is, in part, due to the lack of knowledge about PE, the absence of performing a careful history, and the nonexistence of diagnostic tools for PE [3]. Despite its high prevalence and recognized adverse effects on men’s quality of life, it is only
recently that attention has been focused on investigating the causes of PE and developing new therapeutic strategies.

A universally accepted definition of PE has yet to be established. Various definitions of PE have been used by different researchers, and include partner satisfaction, male voluntary control, duration of ejaculatory latency, and number of intravaginal thrusts [4]. Kaplan first suggested that PE was primarily a problem of voluntary control over timing of ejaculation, a concept on which most of the current definitions are based [5]. According to The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR®), PE is defined as “persistent or recurrent ejaculation with minimal sexual stimulation, and before the subject wishes it” and is associated with “marked distress or interpersonal difficulty” [6]. The American Urological Association Guideline on Premature Ejaculation defines PE as “Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners [3]”.

Premature ejaculation has been classified as either primary (life-long) that begins when a male first becomes sexually active or secondary (acquired), meaning that a male previously had an acceptable level of ejaculatory control and developed the condition later in life [7,8]. Primary PE is hypothesized to have a strong biological component with a variable psychological contribution [9]. Although psychological or situational stressors may contribute to secondary PE, certain medical conditions and medications may also be associated. Another classification invokes the terms “global” or “universal” (e.g., occurs regardless of situation or partner) or “situational” (e.g., limited to certain situations or partner) [10]. Waldinger and Schweitzer also suggested another PE type “Natural Variable PE” which is not a typical syndrome but rather a cluster of inconsistent symptoms of rapid ejaculation and belongs to the normal variability of sexual performance [11].

Selective serotonin reuptake inhibitors (SSRIs) are widely used “off label” as pharmacotherapeutic agents in the treatment of rapid ejaculation. The potential of antidepressants to treat PE was first introduced by Eaton in 1973 [12].

Tramadol [cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol] is a centrally acting synthetic opioid analgesic with a Cmax of 300 μg/L after 100 mg single oral dose [13]. The brand name in the United States is Ultram. It has been prescribed for many years and its safety profile is acceptable. Tramadol’s mode of action is not completely understood. From animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors (antinociceptive effect) and inhibition of reuptake of norepinephrine and serotonin which may stand for its effect on delaying ejaculation. Tramadol’s action on 5-HT1A and 5HT3C needs further investigations.

Safarinejad and Hosseini [14] recently published a double-blind, placebo-controlled, fixed-dose study indicating that on-demand use of 50 mg Tramadol exerted a significant ejaculation delaying effect in men with PE. In the current single-blind, placebo-controlled study in men with PE, we independently investigated the on-demand use of 25 mg Tramadol.

**Methods**

This study included 60 patients with PE, age ranged from 22 to 62 years with mean (36 ± 8.87) treated from September, 2003 to May, 2004. The study was approved by the local medical ethics committee. Patients were recruited by advertisement and consented for participation. PE was defined according to the DSM-IV-TR definition of PE as persistent or recurrent ejaculation with minimal sexual stimulation before, at, or shortly after penetration and before the subject wishes it. All patients had an active sexual life with score ≥22 on the erectile function domain of the International Index of Erectile Function [15]. All patients had primary PE (life-long PE since their first sexual experience).

The intravaginal ejaculation latency time (IELT), with at least one intercourse episode per week, for all patients was <2 minutes in 80% of intercourse attempts in a 4-week test period prior to the start of treatment. This was an inclusion criterion for all the patients in our study.

A single-blind, placebo-controlled, crossover, stopwatch monitored two-period study was conducted with a dose (25 mg, PRN) of Tramadol hydrochloride (T) for one group (30) and placebo for the other group (30) for 8 weeks. After the 8-week trial, patients were instructed to stop treatment for 1 week as a washout period. After the washout period, the two groups took the alternate medication for another 2 months. The drug was required to be taken 1–2 hours before sexual activity and frequency of sexual intercourse episodes was required to be at least once per week. IELT at
each intercourse was reported by patients or partners. Patients were instructed to measure the IELT by stopwatch from the start of penetration to the start of ejaculation by either the patient or the partner. All patients completed the study period.

All patients were asked about their satisfaction with their control over ejaculation with either treatment. No specific validated questionnaire was used in this study. The subjects were asked about satisfaction with their sexual act on either drug with two questions “Are you satisfied with your control over ejaculation with the treatment?”, “Are you satisfied with your sexual act with the treatment?” Patients were also asked about their tolerance to the drug and if there were any side effects.

Intravaginal ejaculation latency time improvement, defined as the difference between IELT at the end of each treatment period and baseline, was selected as the main outcome of interest in the crossover analysis. Presence of a carryover effect was assessed by testing for a significant treatment by period interaction in an analysis of variance (ANOVA) framework. Because there was no evidence of a significant carryover effect, the difference between IELT improvement under Tramadol hydrochloride treatment and placebo treatment (irrespective of the order of administration) was tested by a nonparametric Wilcoxon matched-pairs signed-ranks test. The crossover analysis was performed using the PKCROSS procedure implemented in the Stata statistical package (Stata Corporation, College Station, TX, USA).

**Results**

This study was conducted on 60 patients. All of them had lifelong PE. Four week (pretreatment) data of the IELT by patients showed IELT <2 minutes in more than 80% intercourse attempts. The first 30 patients started with placebo, while the next 30 patients started with Tramadol (Table 1).

The baseline (mean ± SD) IELT for patients before treatment was 1.17 ± 0.39 minutes (range 0.09–1.96), 1.22 ± 0.36 minutes (range 0.68–1.96) for group 1 and 1.11 ± 0.42 minutes (range 0.09–1.92) for group 2. At the end of treatment,

<table>
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<th>Table 1</th>
<th>The baseline IELT before treatment, and with either treatment</th>
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<td>Placebo then Tramadol (group 1)</td>
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IELT = intravaginal ejaculation latency time.
the mean IELT was increased significantly in patients on Tramadol treatment to reach 7.37 ± 2.53 minutes (range 2.68–13.08) (Wilcoxon matched-pairs signed-ranks test, \( P < 0.0001 \)). Patients on placebo showed mean IELT of 2.01 ± 0.71 minutes (range 0.19–4.35) (Table 1). There was a 6.3-fold increase in IELT for Tramadol and 1.7-fold increase for placebo.

In total, 59 of 60 Patients (98%) who received Tramadol reported significant (satisfactory) increases in their control over ejaculation from baseline and significant benefits in their sexual satisfaction (with their sexual intercourse episodes) when taking Tramadol. Only one patient (no. 2) in (group 2) reported that his control over ejaculation was not satisfying for him with either treatment. This patient has had IELT of 1.87 minutes before treatment, 2.05 minutes with placebo, and 2.86 minutes with Tramadol.

All patients were satisfied with their tolerance to the treatment drugs (Tramadol and placebo). However, eight patients (13.3%) reported the experience of mild dyspepsia (5) and mild somnolence (3) with Tramadol. No serious side effects were reported by any patient.

Intravaginal ejaculation latency time improvement was defined as the difference between IELT at the end of each treatment period and baseline. There was no evidence of a significant carryover effect for IELT improvement (\( P = 0.6919 \)). Therefore, whether patients received Tramadol hydrochloride treatment in the first or second period of the crossover trial was ignored, and the effect of Tramadol hydrochloride was compared with that of placebo for all patients. The median IELT improvement for patients while received Tramadol hydrochloride was 5.14 minutes longer than while they taking the placebo. This difference was highly significant (Wilcoxon matched-pairs signed-ranks test, \( P < 0.0001 \)) (Table 2).

### Discussion

Over the past 20–30 years, clinical investigators have participated in a growing number of controlled studies that are developing our basic understanding about PE. The emergence of well-conducted clinical trials has given us knowledge of the prevalence of PE, its etiology and pathophysiology, and additionally, its impact on patient and partner quality of life.

There are currently no regulatory or Food and Drug Administration (FDA)-approved pharmacological therapies for treating PE. Although SSRIs are intended for chronic use in the treatment of depression and are designed to have pharmacokinetic profiles that would allow them to provide constant systemic concentration with long-term administration, it takes about 2–3 weeks to reach a maximum steady-state concentration in order to exhibit efficacy [16]. Therefore, SSRIs are commonly used in a daily dosing schedule for the treatment of PE [3]. In addition to the potentially desirable effect of delaying ejaculation, this dosing regimen for long-acting SSRIs is associated with a number of undesirable side effects, such as decreased libido and ED. With the success of daily SSRI use in delaying ejaculation, it has been suggested that on-demand treatment with SSRIs possessing a short half-life and short Tmax would be equally effective, more convenient, and exhibit fewer serotonergic side effects than that observed with daily treatment. Despite that, there is not much known about the effect of SSRIs with a very short \( T_{\text{max}} \) and short \( T_{1/2} \) on 5-HT neurotransmission [17].

Dapoxetine was the newly developed serotonin transporter inhibitor for the on-demand treatment of PE. The drug was subjected to research studies for pharmacokinetics, pharmacodynamics, and efficacy for the on-demand use. A double-blind,
placebo-controlled crossover phase II study of
dapoxetine for on-demand treatment of PE [18]
showed a mean baseline IELT increase form
1.01 minutes to 2.94 minutes with 60 mg dapoxe-
tine, 3.20 minutes with 100 mg dapoxetine, vs.
2.05 minutes with placebo. In this study, patients
reported a small, statistically significant increase in
their control over ejaculation and expressed bene-
fits in their sexual satisfaction. Although this study
and other research demonstrated potentially en-
couraging results, dapoxetine was considered by
the FDA for approval in the United States and
initially rejected. Its sponsors are conducting
additional trials.

The initial impetus behind this study was our
observations of the effect on sexual function of
patients taking Tramadol for analgesia. The fact
that many of these patients had delayed ejacula-
tion or anejaculation inspired the use of Tramadol
empirically since 2000 in patients with PE. The
second factor was the available data about seroto-
nin syndrome with over dosage of Tramadol, or
combination treatment with Tramadol and SSRIs
[19]. Recently, in February 2006, Safarinejad and
Hosseini [14] published the first study on the on-
demand use of 50 mg Tramadol to treat PE show-
ing a significant effect of 50 mg dosage. In the
current single-blind study, we investigated the
on-demand use of 25 mg Tramadol. Compared
with the study of Safarinejad, we found 6.3-fold
increase in IELT on treatment with 25 mg Tram-
adol compared with 1.7-fold increase with pla-
cepto, while in Safarinejad study, they reported
13-fold increase in IELT with 50 mg Tramadol
which may indicate a dose-dependent effect of the
drug in delaying ejaculation. In this study,
Tramadol seemed to be a very effective drug for
treatment of PE, with increased IELT, improved
control over ejaculation, and increased satisfac-
tion with sexual intercourse. We empirically
selected the use of 25 mg Tramadol for dosage as
this was the lowest dose commonly prescribed as
an analgesic.

Because there is no specific validated question-
naire for PE, we used IELT as an objective method
for follow-up. In addition, patients were specifi-
cally asked about their control over ejaculation and
their satisfaction with the sexual act. A valid crit-
icism of our study is that we did not ask the patients
to complete another validated questionnaire as we
did pre treatment. Our reasoning for this short-
coming was there was no questionnaire that
addressed PE specifically as a cause of sexual
dysfunction.

Despite recent and current clinical investiga-
tions studying on-demand use of newer SSRI
drugs such as dapoxetine, Waldinger et al. [20] has
consistently reported that on-demand SSRI treat-
ment (1–2 hours prior to coitus) is seriously lim-
ited because of counter-regulatory processes of
normal serotonergic neurotransmission. In a sim-
ilar, more recent study, Waldinger concluded that
on-demand SSRI treatment has only a slight ejac-
ulation-delaying effect and is less effective than
prolonged daily treatments [17].

The exact mechanism of action of Tramadol to
delay ejaculation is not known. Its known weak
serotonin and norepinephrine reuptake inhibitory
action is unlikely to be the only explanation for its
effectiveness in patients with PE. Whether it has
other central actions on serotonin receptors needs
further investigations.

Conclusions

This is the second study showing the Tramadol's
impressive results in delaying ejaculation. While
our initial results are encouraging, more studies
are needed on larger scale with different drug
doses. Our demonstration of Tramadol's on-
demand efficacy favors the “off label” use of this
drug in the treatment of PE instead of SSRI anti-
depressants. These preliminary data should stim-
ulate more investigative activity to elucidate its
exact mechanism of action. Furthermore, efficacy
and tolerability studies combining Tramadol with
lower doses of SSRIs and/or phosphodiesterase 5
inhibitors for treatment of PE might also be
enlightening.

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Conflict of Interest: Dr. Salem holds U.S. Patent appli-
cation number 60-759916. Steven K. Wilson is a consult-
ant, investigator, investor for AMS. John Delk is a
consultant, investigator for AMS. Wayne Hellstrom is
a lecturer and consultant for Auxilium; consultant, advi-
sor, lecturer, investigator, scientific study trial for AMS;
consultant, advisor, lecturer, scientific study trial for
Johnson & Johnson/OrthoUrology; consultant, advisor,
lecturer, investigator, scientific study for Lilly ICOS;
consultant, advisor, investigator for Mentor; lecturer,
scientific study trial for Pfizer; consultant, advisor, lec-
turer, investigator for Sanofi-Aventis; consultant, advi-
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