ASSESSMENT OF HEADACHE IN MEN TAKING PHOSPHODIESTERASE-5 INHIBITOR (TADALAFIL) FOR ERECTILE DYSFUNCTION

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ABSTRACT

Aims*: Tadalafil , a selective inhibitor of the cyclic guanosine monophosphate (cGMP) degrading phosphodiesterase 5 (PDE5), is known to cause headache as a secondary effect. This study was undertaken to assess the frequency, clinical characteristics of headache prospectively in a group of erectile dysfunction patients taking tadalafil as a PDE inhibitor.*

Materials and methods*: As the first step of study, the question about "having ever headache in last year" was asked. Of the 31 patients, 16 patients (51.6%) had "yes" as an answer for the presence of headache. A questionnaire was given to the patients who had experienced headache whether recurrent or not. When patients were at headache-free period, tadalafil (20 mg) was administrated to each patient. The question about "having headache" was asked 5 hours and 48 hours later. According to the answer of this question, second questionnaire was conducted. The analysis of questionnaires was made separately. International Classification of Headache Disorders (ICHD) has been used for the case definition criteria.*

Results*: A statistical significant difference was observed for the occurrence of headache between the baseline, 5th and 48th hours (p= 0.001, cochran's Q test). However, we found no significant difference in headache occurrence between fifth hour and 48th hour of tadalafil 20 mg administration (p= 0.687, Mc Nemar test).*

Conclusion: *So from this study, it can be concluded that tadalafil can trigger headache attacks within the half-life of the drug.*

Key words*: Erectile dysfunction, Headache, Phosphodiesterase.*

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Introduction

Tadalafil, Sildenafil and vardenafil are three, well tolerated and effective oral medications that inhibit phosphodiesterase-5 (PDE5) and provide physicians with treatment options for men with erectile dysfunction (ED). Phosphodiesterases are intracellular enzymes involved in cAMP and cGMP degradation. PDE5 inhibitors (PDE5i) exert their effect peripherally by preventing the breakdown of 3',5'-cyclic guanosine monophosphate (cGMP) in penile, smooth muscle, which in turn lower intracellular calcium, promotes relaxation, improves blood volume and causes erection[1]. PDE5i enchance the effect of NO by inhibiting PDE5, which is responsible for the degradation of cGMP in the corpus cavernosum. Since PDE is also found in the brain as well as in the corpus cavernosum , PDE5i may exert side effects in the CNS by crossing the blood-brain barrier[2]. The side effect profiles for PDE5i are nearly identical; headache is the most common side effect[1]. Selective PDE inhibitors have been included as headache triggers in the 2nd edition of the International Classification of Headaches[3]. The incidence of headache, reported by different authors, ranges from 16% to 25% depending on the type of the PDE-5i used[4,5,6].

The goal of this study is to investigate the frequency, clinical characteristics of headache prospectively in a group of ED patients taking tadalafil as a PDE5 inhibitor. As far as we know, there's no study demonstrating this issue.

Material and method

The institutional ethical committee approved the study protocol. Informed consent was obtained from each participant according to the declaration of Helsinki. A total of 34 men with erectile dysfunction admitted to the Department of Urology

were included in the study. All patients were evaluated by the same urologist and neurologist. All subjects have never received PDE-5 inhibitor before inclusion and prestudy screening was performed including medical history, physical examination, cardiovascular examination. Criteria leading to exclusion of the patients screened were cerebrovascular disease, cerebral tumor, traumatic brain injury, clinical of brain scan evidence of focal brain lesions, delirium, hypertension, diabetes mellitus, use of any kind of daily medication, excessive use of analgesics or alcohol, serious somatic or psychiatric disorders, ischemic heart disease.

The patients were headache-free at the beginning of the study and they were told not to take any medication, or consume coffee, tea, alcohol or tobacco for 12 h before study.

The study planned in 2 phases. In phase 1, the patients who had been referred to neurologist after urological examinations, were asked if they had ever experienced headache and if so, whether it had recurred or not. The term headache included all forms of headache. Recurrent headache has been defined as a headache attack occurring more than once a year.

A questionnaire was given to the patients who had experienced headache whether recurrent or not. The followings are questioned in 4 pages: The first page; demographic data, such as age, sex and habits, familial history, neuropsychiatric and systemic disease history. Second page was designed to determine the characteristics of headache: frequency, triggering enhancing factors, duration with and without treatment, location characteristics, type of onset, symptoms of aura, prodrome and signs, performing daily activities during headache. Third page; systemic and neurological characteristics. Fourth page; treatment and follow up. In phase 2, tadalafil 20 mg was administered orally. At administration all patients were headache free. At fifth and 48th hour, all the patients were asked if they had experienced headache after the drug was intaken. Patients answering ''yes'' were requested to answer the second and third page of the questionnaire again. In all phases, the analysis of questionnaires for each phase was made separately by the same neurologist (E.O). The specific criteria has been used for the diagnosis of 'phosphodiesterase inhibitor-induced headache(8.1.2)' involved in International Classification of Headache Disorders (ICHD). Additionally, ICHD has been used for the case definition.

Necessary investigations and examinations were done when secondary headache was suspected.

Power of the study

Several authors have reported various percentages of headaches (16-25%) considerably, depending on the type of PDE5-I[4,5,6]. These previous studies were the background information used to calculate the sample size. Because the half life of tadalafil is longer than the other PDE5-inhibitors, we postulated that the incidence of headache might be closer to the upper limit of this range. Therefore, for sample size calculation, the values used were based on the literature published during the time the study was conducted , and from these, we assumed a headache incidence of 25% with tadalafil[4,5,6]. With a sample size calculator (DSS Research, Fort Worth, TX, USA), it was estimated that 30 patients were needed to give this study a power of 90% with a 95% confidence interval.

Statistical methods:

Statistical analysis was performed with SPSS 16.0 (SPSS Inc, Chicago, USA). Analyses were performed on data from the intent-totreat population. The categorical variables were summarized by using ratio and percentages. The continuous variables were summarized with descriptive statistics including; mean, standard deviation, median, minimum. Comparisons between measurement times were done with Cochran's Q test for the dichotomal variables. If there were significant differences between measurement times, subgroup analysis were tested with McNemar test. For nominal variables, comparisons between groups were done with x2 tests. Statistical significance was defined as $p < 0.05$.

Results and discussion

Of the thirty-four patients included in the study, two patients with hypertension, one patient with diabetes mellitus and one patient with cerebrovascular disease were excluded during the study. The remaining 31 patients were between the ages of 30 to 75 years (mean 54.5 ± 11.3). Before the drug administration, 16 (51.6%) out of 31 patients had "yes'' and 15 (48.4%) patients had ''no'' as an answer for the presence of previous headache. According to ICHD-II criteria, tension type headache was identified in 12 patients (38.7%). Of the twelve patients, 7 (22.6%) were regarded as

infrequent episodic tension type headache, whereas 5 (16.1%) were defined as chronic tension type headache. Migraine was detected in 4 patients (12.9%), one patient (3.2%) had migraine with aura and three patients (9.7%) had typical migraine without aura. At the second stage of the study, the drugs (tadalafil, 20 mg) were intaken by the patients when they were headache free. Five hours later, 10 patients (32.3%) out of 31 patients had headache. Tension type headache was identified in 6 (19.4 %) patients. Four patients (12.9%) had migraine attack. Of the four patients, migraine with aura was detected in one patient (3.2%) while migraine without aura in three patients (9.7%). At 48th h, 8 patients (25.8%) out of 31 patients had headache. Tension type headache was identified in 4 (12.9%), whereas 4 patients (12.9%) had migraine type headache. Migraine with aura was detected in one patient (3.2%) while 3 (9.7%) patients had typical migraine without aura. A migraine attack was provoked in all four patients with a history of migraine whereas a tension type headache was provoked in half of the patients. All these data were summarized on Table I.

	Prior To Study		5th hour of tadalafil 20 mg administration		48th hour of tadalafil 20 mg administration	
	n	%	n	%	n	%
Migraine with Aura	1	3.2	1	3.2	1	3.2
Migraine without Aura	3	9.7	3	9.7	3	9.7
Tension Type Headache	12	38.7	6	19.4	4	12.9
Headache-free	15	48.4	21	67.7	23	74.2
Total	31	100.0	31	100.0	31	100.0

Table 1: Frequency of Headache Types Before and After Drug Administration.

A statistical significant difference was observed for the occurrence of headache between the baseline, 5th and 48th hours (p= 0.001, cochran's Q test). However, we found no significant difference in headache occurrence between second hour and 48th hour of tadalafil 20 mg administration (p= 0.687, Mc Nemar test). Neither was a difference found in headache location (unilateral or bilateral) between 5th and 48th hour of tadalafil 20 mg administration (p=0.368, cochran's Q test).

The clinical characteristics of headache at admission (previous headache) and at fifth hour and 48th hour of drug administration were summarized on Table II.

Characteristics	Prior to Study		5h after tadalafil		48h after tadalafil	
Location	n	(%)	n	(%)	n	(%)
Frontal	7	(22.6%)	7	(22.6%)	6	(19.4 %)
Temporal	4	(12.9%)	0	(0%)	0	(0%)
Occipital	4	(12.9%)	1	(3.2%)	2	(6.5%)
Holocranial	1	(3.2%)	1	(3.2%)	0	(0%)
Other	0	(0%)	1	(3.2%)	0	(0%)
Unilateral	8	(25.8%)	5	(16.1%)	4	(12.9 %)
Bilateral	8	(25.8%)	5	(16.1%)	4	(12.9%)
Quality						
Throbbing	1	(3.2%)	2	(6.5%)	1	(3.2%)
Pressurelike	4	(12.9%)	0	(0%)	2	(6.5%)
Sharp	2	(6.5%)	0	(0%)	0	(0%)
Pulsating	7	(22.6%)	8	(25.8%)	5	(16.1%)
Other	2	(6.5%)	1	(3.2%)	0	(0%)
Duration						
Seconds-30min	3	(9.7%)	0	(0%)	0	(0%)
30 min - 2h	5	(16.1%)	2	(6.5%)	0	(0%)
> 2h	3	(9.7%)	1	(3.2%)	3	(9.7%)
Other	5	(16.1%)	7	(22.6%)	5	(16.1%)
Nousea						
Present	5	(16.1%)	3	(9.7%)	2	(6.5%)
Absent	11	(35.5%)	7	(22.6%)	6	(19.4%)
Vomiting						
Present	5	(16.1%)	4	(12.9%)	3	(9.7%)
Absent	11	(35.5%)	6	(19.4%)	5	(16.1%)
Premonitory Symptom						
Present	1	(3.2%)	1	(3.2%)	0	(0%)
Absent	15	(48.4%)	9	(29.0%)	8	(25.8%)

Table 2: Headaches Characteristics.

In this study our main goal was to appraise the acute effect of PDE inhibitors on headache characteristics and the headache frequency in patients with ED. As far as we know, this study, which was performed on a face-to-face interview basis with ED patients taking drug is to be the first study on this issue.

Phosphodiesterases are intracellular enzymes responsible for the degradation of the second messangers cAMP and cGMP. The most likely mechanism of action for PDE inhibitors seems to be intracellular cGMP elevation. Tadalafil, a specific PDE 5 inhibitor, is rapidly absorbed with maximal plasma concentrations occurring within 2 hours after

oral administration with a mean terminal half-life of 17 to 18 hours and its efficacy is more than 36 hours. Intracellular increase of cGMP in smooth muscle cells and enhancement of relaxation by NO occurs well within this plasma concentration of tadalafil. Headache, which develops within 5 hours and resolves within 72 hours of PDE-5i intake, is accepted as "PDE inhibitor induced headache" according to the specific diagnostic criteria of ICHD. Thus, to observe the acute effect of drug and the presence of headache was asked at 5th and 48th hour after ingestion.

The role of various signaling molecules in migraine and headache pathology has not been reached yet[7]. However, the intercellular signalling molecule nitric oxide (NO) and the neuropeptide calcitonin gene-related peptide (CGRP) are believed to play an important role in the pathophysiology of migraine[8,9]. CGRP appears to activate endothelial NO synthase to cause further NO production which leads to dilatation of blood vessels[10,11]. NO is proposed to induce headache either by stimulating pain-sensitive nerve fibers around cerebral arteries or by arterial dilatation[12]. NO increases intracellular cyclic guanosine monophosphate (cGMP) by stimulation of soluble guanylate cyclase in smooth muscle cells or neuronal cells. The elevation of cGMP levels in neuronal cells increase neuronal excitability[13,14]. Plasma cGMP level was increased during migraine attacks in 37 patients with migraine compared with 40 normal subjects and was reported to decrease in response to sumatriptan[15]. But, cGMP levels were not correlated to clinical signs and pain intensities.

Dipyridamole, an adenosine re-uptake inhibitor and a lesser selective inhibitor of PDE5 than tadalafil, induces headache probably concomitant to a dilatation of large cerebral arteries in healthy subjects, however there was a temporal dissociation between headache and arterial dilatation. The effect that was responsible for the headache was due to the mechanisms related to cyclic nucleotides, either directly by increased cGMP or indirectly by adenosine-stimulated increase in cAMP[16].

Recently two studies were performed about the effects of sildenafil on headache, cerebral blood flow, and artery dilatation[17]. In these studies, sildenafil used as a tool to investigate the role of endogenously produced cGMP as part of the nitric oxide-cGMP cascade in headache induction.

The target tissue in headache induction might be either the vascular smooth muscle cells or neuronal cells, because of the lack of haemodynamic effects, suggesting a central mechanism[7]. Since vardenafil and tadalafil have the same effect profile and mechanism of action with sildenafil, they likely have the same effect. But there is not any study using either vardenafil or tadalafil.

In previous studies, there was a lack of focus on headache, so we aimed to analyze the clinical characteristics of tadalafil-induced headache. The occurrence of headache after drug ingestion was significantly increased at 5th and 48th hour when compared with baseline. However there was no significant difference in headache occurancy between 5th and 48th hour. There were four patients known to be with migraine before the drug administration. All of them had migraine attack approximately at the 5th hour of drug administration and, they still had headache at the 48th hour. But none of the four patients had new migraine attack, their headaches were the prolonged form of the first attack. In parallel to our study, Kruuse et al have studied the effects of sildenafil in migraine sufferers. It did not cause any change in cerebral blood flow or cerebral artery diameter, but induced migraine attacks[7]. Theorically, tadalafil, has the longest half-life, could induce longer lasting migraine or an increased risk of recurrent migraine just like our 4 patients.

The results of the study indicate that 50% of the tension type headache patients developed a tension type headache 5 hours after administration of tadalafil. This result is consistent with the findings that suggest headache due to PDE-5i may be represented as tension type headache[18]. Underlying pain mechanisms in tension type headache differs, not just between the subjects, but also within the individual subject over time. The initiating stimulus may be either a condition of mental stress, motor stress, a local irritative process with release of various mediators, or a combination of these[19]. The NO-cGMP signaling pathway was supposed to regulate serotonin depletion not only in the periphery but also in supraspinal inhibitory pathways involved in head pain processing. It can be expected that the hyposerotonergic status may be related to central sensitization of headache in patients with tension type headache[20].

Conclusion

It seems that, tadalafil triggers headache not only in patients with migraine but also in patients with tension type headache in a given dose of 20 mg. Considering the headache-inducing effects of tadalafil and the other PDE-5 inhibitors, unless the drug companies provide data proving otherwise, patients should be made aware of the risk of inducing a headache attack before initiation of treatment with PDE-5 inhibitors.

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