Cases detected with sildenafil/tadalafil/vardenafil in autopsies performed in Muğla: retrospective evaluation

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Abstract

Cases detected with sildenafil/tadalafil/vardenafil in autopsies performed in Muğla: retrospective evaluation

Objective: In this study, it was aimed to discuss the cases that were detected with phosphodiesterase 5 (PDE-5) inhibitors in autopsies performed, the mechanisms that may affect death, the aspects to be paid attention and protective measures in autopsy of these cases, and to investigate whether the use of PDE-5 inhibitors has cardiac side effects.
Materials and Methods: Cases in which PDE-5 inhibitors were found in body fluids in toxicological examinations among autopsies performed in the 8-year period between January 01, 2013 and December 31, 2023 in Mugla Forensic Medicine Branch Office were retrospectively evaluated.
Results: Sildenafil/vardenafil/tadalafil were detected in 49 (0.9%) of 5,277 autopsy cases. Sudden/suspicious deaths were the most common reason for sending the cases to autopsy. This was followed by drowning, traffic accidents and hangings, respectively. The most common cause of death in cases using PDE-5 inhibitors was atherosclerotic cardiovascular disease/ myocardial infarction (n:22, 44.8%).
Conclusion: In our study, it was determined that more than 44.8% of the cases with PDE-5 inhibitors in the autopsy had cardiovascular diseases. It suggests that PDE-5 inhibitors may have caused risky cardiac side effects. It is considered that the present study will contribute to the literature in terms of showing the cardiac side effects of PDE-5 inhibitor.
Keywords: Postmortem toxicology, Sildenafil, Autopsy

Öz

Muğla'da yapılan otopsilerde saptanan sildenafil/tadalafil/vardenafil olguları: retrospektif değerlendirme

Amaç: Bu çalışmada otopsilerde fosfodiesteraz 5 (PDE-5) inhibitörleri tespit edilen olguların, ölüme etki edebilecek mekanizmalarının, otopsilerinde dikkat edilmesi gereken hususların ve alınabilecek koruyucu önlemlerin tartışılması; ayrıca PDE-5 inhibitörlerinin kardiyak yan etkilerinin olup olmadığının araştırılması amaçlanmıştır.
Gereç ve Yöntem: 01 Ocak 2013 – 31 Aralık 2023 tarihleri arasında Muğla Adli Tıp Şube Müdürlüğü'nde yapılan otopsiler arasında, toksikolojik incelemelerde vücut sıvılarında PDE-5 inhibitörleri saptanan olgular retrospektif olarak değerlendirilmiştir.
Bulgular: 5.277 otopsi olgusunun 49'unda (%0,9) sildenafil/vardenafil/tadalafil tespit edilmiştir. Olguların otopsiye gönderilme nedenleri arasında en sık ani/şüpheli ölümler yer almıştır. Bunu sırasıyla boğulmalar, trafik kazaları ve asılar izlemiştir. PDE-5 inhibitörleri kullanan olgularda en sık ölüm nedeni aterosklerotik kardiyovasküler hastalık / miyokard enfarktüsü (n:22, %44,8) olarak bulunmuştur.
Sonuç: Çalışmamızda, otopsilerde PDE-5 inhibitörleri saptanan olguların %44,8'den fazlasında kardiyovasküler hastalık olduğu belirlenmiştir. Bu bulgu, PDE-5 inhibitörlerinin riskli kardiyak yan etkilere yol açmış olabileceğini düşündürmektedir. Mevcut çalışmanın PDE-5 inhibitörlerinin kardiyak yan etkilerini göstermesi açısından literatüre katkı sağlayacağı değerlendirilmektedir.
Anahtar Kelimeler: Postmortem Toksikoloji, Sildenafil, Otopsi

INTRODUCTION

Oral Phosphodiesterase-5 (PDE-5) inhibitors are first-line drugs used in the treatment of erectile dysfunction. Three different PDE-5 inhibitors, sildenafil, tadalafil and vardenafil, that are used in clinical practice are available. These drugs strengthen the erection during sexual stimulation by allowing the corpus cavernosum smooth muscle to relax (1).

Side effects of all three drugs are similar and are usually transient and of mild to moderate severity. However, patients with moderate and severe cardiovascular disease who use nitrates and alpha-blockers are under potentially high risk in terms of serious cardiovascular side effects (2). In the high-risk cardiovascular disease population, the presence of acute coronary syndrome, high-risk arrhythmia, hypertrophic obstructive cardiomyopathy, moderate or severe heart valve disease and congestive heart failure or hypotension as well as the use of three or more antihypertensives (uncontrolled hypertension) and nitrate-containing drugs are observed. Sildenafil use is risky in patients in this population. Additionally, patients who receive drugs that inhibit the cytochrome P450 3A4 isozyme that metabolizes sildenafil can have elevated drug concentrations and possible toxicity due to normal sildenafil doses (3). It has been reported that vardenafil prolongs the QT interval, causes ventricular arrhythmias, and should not be used in combination with antiarrhythmic agents (4).

No consistent data are available indicating that sildenafil induces acute coronary syndrome or any other serious cardiovascular disease in normal healthy individuals. In a normal healthy individual, following sildenafil intake, a moderate and transient decrease of 7-9 mmHg in blood pressure occurs, while there is no significant change in heart rhythm and heart rate (5). Besides, it has been indicated in a study that sildenafil increases parasympathetic activation and that since increased parasympathetic activation is known to be protective against malignant arrhythmia and sudden cardiac death, sildenafil citrate does not carry a cardiac risk in this regard (6).

It has been reported that about one-fourth of patients with erectile dysfunction use PDE-5 inhibitor without physician recommendation, some of them also use drugs such as alpha-blockers and nitrate, the use of which is contraindicated when combined with PDE-5 inhibitors (7).

PDE-5 inhibitor drugs can also be used in the treatment of pulmonary hypertension, idiopathic pulmonary fibrosis and some ophthalmological diseases, other than the treatment of erectile dysfunction (8-10). On the other hand, serious cardiovascular events such as ventricular arrhythmia, myocardial infarction, cardiac arrest, transient ischemic attack and hypotension have been reported to be temporally associated with the use of sildenafil. Especially in the use of non-prescription drugs, it is difficult to ensure safety in risky individuals. The sale of these drugs on the streets or their easy accessibility through websites poses a risk to public health.

In this study, where the autopsy reports of cases whose autopsies were performed in the Muğla Forensic Medicine Branch Directorate between 2013-2023 and sildenafil/vardenafil/tadalafil were found in the toxicological examination, were retrospectively examined, it was aimed to evaluate the correlations between cardiovascular pathologies and toxicological results detected in the autopsy of cases where PDE-5 inhibitors were used, to examine the possible consequences of these drugs, whose use is widespread without a prescription, in individuals in the risk group, to create awareness in terms of public health and to discuss protective measures.

MATERIAL AND METHOD

Among the autopsies performed in the 8-year period between January 01, 2013 and December 31, 2023 in Mugla Forensic Medicine Branch Directorate, cases in which PDE-5 inhibitors were found in body fluids in toxicological examinations were retrospectively reviewed. The reports of the cases were evaluated in terms of age, sex, autopsy date, macroscopic and microscopic findings, toxicological analysis results, scene investigation and cause of death. LC/MS/MS method was used for drug detection in blood. The data obtained were analyzed by using a statistical software package; frequency and percentage analyses were performed and the data were presented in tables.

Approval was obtained from the scientific committee of the Institute of Forensic Medicine for the study to be conducted. The data does not contain personal information. Since it is a retrospective study, there are some shortcomings such as the medical history of the cases, information on prescription drug use, and the small number of cases.

RESULTS

A total of 5,277 autopsies were performed in Mugla Forensic Medicine Branch Directorate between the dates of January 01, 2013 and December 31, 2023, and sildenafil, tadalafil or vardenafil was detected in 49 cases (0.9%) in toxicological examinations. Of the cases, there were 47 (95.9%) males and two (4.1%) female. The sole female case was a 13-year-old child with foreign nationality whose body was pulled out of the water. The reason for her use of sildenafil could not be determined since her forensic investigation file was not reached. The distribution of cases by years is displayed in Table 1. The highest number of cases was observed in 2022 (18.4%) and followed by in 2020 and 2023 (16.3%).

Table 1. The distribution of cases by years		
Year	Number of cases	
	n	%
2015	5	10.2
2016	3	6.1
2017	2	4.1
2018	4	8.2
2019	7	14.3
2020	8	16.3
2021	3	6.1
2022	9	18.4
2023	8	16.3
Total	49	100.0

When the cases were classified according to age, it was determined that there were 2 (4.08%) case in the 0-18 years age group, 14 (28.5%) cases in the 18-44 age group, 16 (32.6%) cases in the 45-59 age group, 14 (28.5%) cases in the 60-74 age group and 3 (6.1%) case in the 75-89 age group. The mean age of the cases was 51.5 years. Among the reasons for sending the cases to autopsy, sudden/suspected deaths were in the first place, which were followed by drowning, traffic accident and hanging. The distribution of the cases by the reasons for sending them to autopsy is shown in Table 2.

Concomitant medicines detected in the toxicological analysis of the cases are illustrated in Table 3. The most frequently observed concomitant drug active substances were SSRI (selective serotonin reuptake inhibitors) and antidiabetics (Metformin, gliclazide). More than one medicine was found in some cases.

Substances were also detected in some cases. Opioid (codeine,morphine)(n:4), amphetamines (MDA, MDMA, MDAE, methamphetamine)(n:4), cocaine(N:2) and tetrahydrocannabinol(n:4) were found in a total of 14 cases in the toxicological analysis performed.

Table 2. Reasons for sending the cases to autopsy		
Incident	Number of case	
	n	%
Sudden/suspected deaths	32	65.3
Drowning	3	6.12
Firearm injury	3	6.12
Traffic accident	4	8.16
Removal from fire	1	2.04
Hanging	4	8.16
Electric shock	1	2.04
Intoxication	1	2.04
Total	49	100.0

Table 3. Drug active substances detected in the toxicological analysis of the cases			
Drug active substance	n	Drug active substance	n
Antidiabetics	9	Antihypertensives	2
Paracetamol/acetaminophen	9	General Anasthetics	1
Lidocaine/prilocain	7	Hidrroxyzine	1
Metoclopramide	6	Moxifloxacin	1
Benzodiazepines	5	Dobutamine/epinephrine	1
SSRI	5	Rocunorium	1
Amiodarone	4	Promethazine/pheniramine	1
Antiepileptics	4	Moxifloxacin	1
ʙ-blockers	4	Promethazine/pheniramine	1
PPI	4	Tramadol	1
Antiepileptic	4	Salbutamol	1
Nifedipine/amlodipine	3	Scopolamine	1
Diclofenac/etodolac	3	Pseudoefedrin	1
Atorvastatin	2	Amitriptyline	1
Quetiapine/Olanzapine	2		
Trazodone/venlafaxine	2		

Table 4. Substances detected in the toxicological analysis of the cases	
Substance	n
Morphine/Codeine	4
Cocaine	2
Amphetamines	4
THC/marijuana	4

Alcohol above 10 mg/dl was determined in 18 (36.7%) cases. Ethyl alcohol level of above 250 mg/dl, which is considered a life-threatening condition, was found one case.

The most frequent death cause of the cases using PDE-5 inhibitor was atherosclerotic cardiovascular disease/myocardial infarction (n:22, 44.8%). Death causes of the cases are shown in Table 5. Death cause of two cases was not identified.

Table 6 shows the type and concentration of PDE inhibitor detected in the blood of each case. Sildenafil was detected in 35 cases, tadalafil in 13 cases, and vardenafil in 1 case. The highest concentration of sildenafil detected was 111ng/ml and the cause of death was hanging. The lowest level of sildenafil detected was 1ng/ml and the cause of death was subarachnoid hemorrhage. The therapeutic range of Sildenafil is 0.050–0.500 µg/mL [11]. In 12 cases, the concentration of sildenafil was determined within the therapeutic range.

Table 5. Distribution of the cases by death cause

Death cause	Number of case	
	n	%
Atherosclerotic cardiovascular disease/ myocardial infarction	22	44.8
Susbstance intake	4	8.1
General body trauma and complications	4	8.1
Hanging	4	8.1
Firearm injury	3	6.1
Pathological cerebral hemorrhage	2	4.08
Aspiration of food and vomit	2	4.08
Asphyxia due to drowning	2	4.08
Heart failure + drug intoxication	1	2.04
Burn and carbon monoxide poisoning	1	2.04
Gas poisoning	1	2.04
Natural death by disease	1	2.04
Electric shock	1	2.04
Pneumonia	1	2.04
Total	49	100

The highest level of tadalafil detected was 245ng/ml and the cause of death was firearm injury. The lowest tadalafil level was also 5ng/ml. The therapeutic range of tadalafil have not been established in the litherature. In two cases, although sildenafil was detected at the scene, it was not detected in the blood during toxicological analysis.

Table 7 shows the concentractions of drugs and substances in the blood and histopathological findings of death cases due to cardiovascular diseases. Sildenafil was detected in 15 cases, tadalafil in 6 cases, and vardenafil in 1 case. In 7 cases, the concentration of sildenafil was determined within the therapeutic range.

DISCUSSION

An important part of autopsies performed in Turkey are conducted to determine the causes of sudden and suspected deaths. The fact that sudden deaths is mostly of cardiac reasons requires to examine drugs that may have cardiovascular side effects (12).

Of the total 5,277 cases underwent autopsy in Mugla Forensic Medicine Branch Directorate between 2013 and 2023, PDE-5 inhibitor was detected in 49 (0.9) cases. For this reason, in the present study, it was aimed to reveal the characteristics of the cases with PDE-5 inhibitor detected at the autopsy.

In our study, one case was female, the rest were male. The female case was found to be a child who drowned due to boating accident during migrant smuggling, but no further comment was made because her investigation file could not be reached. The mean age of the cases was 51.5 years and the use of PDE-5 was most common in the 45-59 age group

(n:16, 32.6%). 17 cases were 60 years of age or older. Studies in the literature indicate that the frequency of ED and the rate of sildenafil use increase with age. The age interval in the present study was found to be compatible with the literature in general (7, 13).

PDE-5 inhibitors are first-line drugs used in the treatment of erectile dysfunction. Several studies investigating the effect of sildenafil on mortality have been published in recent years. In these studies, it has been reported that in the majority of cases, sildenafil was not an extra risk factor for acute coronary syndrome or sudden cardiac death in those with no underlying cardiovascular disease (5, 14). On the other hand, a great majority of patients with erectile dysfunction carry cardiovascular risk factors such as hypertension, hyperlipidemia, smoking, diabetes and obesity. This may be a reason that may increase the risk for developing acute coronary syndrome during or immediately after sexual activity in patients treated with sildenafil (14). Due to frequent detection of sildenafil in autopsies of sudden/suspicious death cases, most studies have focused on whether sildenafil can cause sudden death (3, 5, 7, 11, 14, 15). In the first 11-month period following its introduction into market in the United States, the effect of sildenafil on mortality was investigated by the US Food and Drug Administration (FDA), and 130 deaths were reported. Cardiovascular events occurred in 77 of these deaths and stroke in 3. Death occurred 4-5 hours after the use of sildenafil in 43 cases, 29 of whom died during or shortly after sexual intercourse. The mean age of cases was 64 years, and it was determined that 73% had at least one cardiovascular risk factor (15). It has been reported that the use of sildenafil carries risks that could lead to sudden cardiac deaths for patients with underlying cardiovascular disease who use alpha-blocker and nitrate (2). In our study, the presence of moderate to severe atherosclerotic cardiovascular disease was determined macroscopically and histopathologically in the autopsy of 33 cases. This finding also supports that the use of sildenafil in those with underlying cardiovascular disease causes sudden cardiac problems.

Although it has been reported that there is no evidence of sildenafil causing sudden cardiac death in normal individuals, it is considered that unconscious widespread use of drugs without physician control may be risky in patients with underlying cardiovascular pathology (7). The possibility that sildenafil use may cause sudden deaths in individuals with high-risk cardiac disease should not be overlooked. In this study, the most common death cause was determined to be atherosclerotic cardiovascular disease. The histopathological findings of these cases include findings such as perivascular fibrosis, hypertrophy, and atherosclerosis in the coronary arteries, suggesting chronic heart disease, and accordingly, the possibility of PDE-5 inhibitor effecting death in these cases may be increased.

Table 6. (PDE-5) inhibitors and substances concentrations in the blood of the cases and causes of death

Case Number	PDE inhibitors	Concentration (ng/ml)	Cause of death
1	Sildenafil	7	Burn
2	Sildenafil	1	Subarachnoid hemorrhage
3	Sildenafil	175	Heart failure
4	Sildenafil Ethanol	32 30	Heart failure
5	Tadalafil Ethanol	193 260	Firearm injury
6	Sildenafil Ethanol	20 43	Natural death by disease
7	Vardenafil	10	Heart failure
8	Sildenafil THC-COOH Ecgoninemethylester Methylecgonine Benzoylecgonine	65 25	Substance intake
9	Sildenafil	4	Heart failure
10	Sildenafil Ethanol	5 157	Pathological cerebral hemorrhage
11	Sildenafil	40	Heart failure
12	Tadalafil Ethanol THC-COOH	5 136 8	Substance intake
13	Tadalafil Ethanol	5 27	General body trauma and complications
14	Tadalafil	200	Asphyxia due to drowning
15	Sildenafil Ethanol MDA MDMA MDEA	25 15 5 28 5	Heart failure + drug intoxicationw
16	Tadalafil Ethanol	6 93	Hanging
17	Sildenafil	60	Heart failure
18	Sildenafil Ethanol THC-COOH Amphetamine Methamphetamine	250 50 14 25 30	Substance Intake
19	Sildenafil	Not detected	Heart failure
20	Sildenafil	5	Heart failure
21	Tadalafil	5	Heart failure
22	Sildenafil	40	Electric Shock
23	Sildenafil	5	General body trauma and complications
24	Tadalafil Ethanol THC-COOH Cocaine Benzoylecgonine Ecgoninemethylester	20 43 5 20 100 5	Myocardial infarction
25	Tadalafil	20	Heart failure
26	Sildenafil	350	Heart failure
27	Tadalafil Ethanol	213 247	Hanging
28	Tadalafil	20	Heart failure
29	Tadalafil Ethanol	120 21	Heart failure
30	Sildenafil Ethanol Amphetamine Methamphetamine	30 17 5 35	Substance Intake
31	Sildenafil	50	Pneumonia
32	Tadalafil	71	Heart failure
33	Sildenafil	235	Gas poisoning
34	Sildenafil	76	Aspiration of food and vomit
35	Tadalafil Ethanol	245 207	General body trauma-Traffic accident
36	Sildenafil Ethanol Metamfetamin Amfetamin	183 108 738 108	Firearm injury
37	Sildenafil Ethanol	1111 40	Hanging
38	Sildenafil Ethanol	25 61	Heart failure
39	Sildenafil	33	Firearm injury
40	Sildenafil	35	Heart failure
41	Sildenafil	55	Heart failure
42	Sildenafil	12	Aspiration of food and vomit
43	Sildenafil Ethanol	27 58	Hanging
44	Sildenafil	60	Heart failure
45	Sildenafil	138	General body trauma-Traffic accident
46	Sildenafil	212	Heart failure
47	Sildenafil	4	Heart failure
48	Sildenafil	Not detected	Heart failure
49	Sildenafil	Not detected	Myocardial infarction

Ethanol:mg/dl

Table 7. Toxicological and cardiac histopathological findings in deaths due to cardiac diseases

Drugs and substances detected in the blood	Concentration (ng/ml)	Histopathological findings
Sildenafil	175	Myocardial infarction findings consistent with 7-10 days, perivascular fibrosis, hypertrophy, atherosclerosis in coronary arteries
Sildenafil Ethanol	32 30	Areas of scarring in the myocardium,
Pantoprazole Vardenafil	200 10	The heart is large and hypertrophic, atherosclerosis of the coronary arteries and aorta, scarring of the myocardium,
Metformin Sildenafil COHb	4 4 %3.5	Atherosclerosis of the coronary arteries and aorta, scarring of the myocardium
Sildenafil	40	The heart is large and hypertrophic, atherosclerosis of the coronary arteries and aorta, scarring of the myocardium,
Ethanol MDA MDMA MDEA Amiodarone Sildenafil	15 5 28 5 25 25	Atherosclerosis of the coronary arteries and aorta, scarring of the myocardium and papillary muscles
Metoclopramide Pantoprazole Sildenafil	35 680 60	The heart is large and hypertrophic, atherosclerosis of the coronary arteries, scarring of the myocardium,
Etanol THC-COOH Amphetamine Methamphetamine Sildenafil	50 14 25 30 250	Atherosclerosis in the coronary, scarring in the myocardium and papillary muscles, infarction findings consistent with the first 24 hours
Sildenafil	5	The heart is large and myocardial hypertrophy and scarring, atherosclerosis in the coronary arteries and aorta,
Citalopram/Escitalopram Propyphenazone Atropine Tadalafil Paracetamol Metoprolol Pregabalin	15 5 10 5 10 10 -	Large heart, epicardial hemorrhage, myocardial hypertrophy and scarring, atherosclerosis in coronary and aorta, bypass findings
Ethanol Paracetamol Diclofenac Doxepine Tadalafil Quetiapine Moxifloxacin	33 10 95 20 10 190 30	Coronary atherosclerosis, myocardial scarring, infarction findings consistent with 12-24 hours
Ethanol THC-COOH Cocaine Benzoylecgonine Ecgoninemethylester Tadalafil	43 5 20 100 5 20	The heart is large and hypertrophic heart, coronary atherosclerosis, myocardial scarring and hypertrophic muscle fiber,

Ethanol:mg/dl

Table 7. Toxicological and cardiac histopathological findings in deaths due to cardiac diseases (Continue)

Drugs and substances detected in the blood	Concentration (ng/ml)	Histopathological findings
Gliclazide Tadalafil Metformin Metoprolol	100 20 5 5	Interstitial perivascular fibrosis in the myocardium, hypertrophic muscle fibers, atherosclerosis in the aorta and coronary
Sildenafil Paracetamol Atorvastatin	350 230 60	Atheromatous plaque in the coronary artery with mild lumen narrowing, edema and bleeding areas in the lungs
Tadalafil Ethanol	120 21	Scarring and granulation tissue in the myocardium, hypertrophic muscle fibers, atheroma plaque in the coronary artery that narrows the lumen to a great extent,
Tadalafil Lansoprazol Metformin	71 265 19	Focal scarring in the myocardium, interstitial and perivascular fibrosis, coronary arteries 70-80% stenosis
Sildenafil Ethanol Gliklazid Metformin	25 61 2700 184	Scar areas secondary to previous ischemia, 95-98% of coronary lumen narrowing atheroma plaque
Sildenafil Naproksen Lidokain Ketoprofen Amlodipin Etodolak	35 24724 55 32 11 1	Perivascular interstitial fibrosis, hypertrophic muscle fibers
Sildenafil Metformin Amlodipin Metoprolol	55 86 26 1	Scarring due to previous myocardial infarction, moderately narrowing atheroma plaques in coronary arteries, thrombus
Sildenafil Naproxen Citalopram	60 19071 84	Perivascular interstitial fibrosis, atheroma plaque causing 60-70% stenosis in coronary arteries, intraplaque hemorrhage, thrombus
Sildenafil Metformin Hidroklorotiyazid Atorvastatin	212 2766 280 48	Previous myocardial infarction, advanced coronary stenosis
Sildenafil	4	Perivascular interstitial fibrosis, atheroma plaque causing 60-70% stenosis in coronary arteries,

Ethanol:mg/dl

It has been reported that patients who receive drugs that inhibit the cytochrome P450 3A4 isozyme that metabolizes sildenafil may experience elevated drug concentrations and possible toxicity from normal sildenafil doses (3). In the present study, in the toxicological analyses of cases performed, the most common concomitant drug active substance was SSRI group drugs, whereas alpha blockers and nitrates were detected none of the cases. Especially SSRI and PPI group drugs are known to inhibit cytochrome P450 3A4 isozyme, these drugs, which were detected in eight cases in the current study, may have increased the possibility of side effects by slowing down sildenafil metabolism. Sildenafil was detected within the therapeutic range in 12 cases, one case it was over the therapeutic range and other cases was below this range. Sildenafil was detected in the therapeutic range in 7 cases with the cause of death from cardiovascular disease. In these cases, sildenafil may have played a role in the death. In people

with cardiovascular risk factors, side effects may occur in the therapeutic range depending on individual factors. 245ng/ml sildenafil was detected in the blood of a case with acute myocardial infarction findings. On the other hand, sildenafil independent of its level in the blood may have been effective in the occurrence of death in risky individuals (11). In death cases due to cardiovascular diseases, tadalafil and vardenafil have been detected, except for sildenafil. However, since there is not enough information in the literature about the therapeutic and toxic levels of these drugs, no comment can be made on their levels. Tadalafil, initial dose, 10 mg orally no more than once daily; may increase to 20 mg or decrease to 5 mg, based on efficacy and tolerability; maximum: 20 mg daily.

In 8 cases, PDE-5 inhibitors were accompanied by antidepressant drugs. These drugs are known to cause sexual dysfunction, and patients may need to use PDE inhibitors. However, it is not known whether the PDE inhibitor was used prescription or non-prescription and uncontrolled, with the available data.

In the literature, the use of PDE-5 inhibitors together with narcotic substances for recreational purposes in social environments has also been reported (4). Attention has been called that sildenafil are frequently used in combination with MDMA and methamphetamine in the United States and Canada (16). A study conducted in England indicated that opiate addicts in particular obtain sildenafil from street sources or over the internet to enhance sexual performance, which is adversely affected by long-term use of opiates (17). It has been reported that the use of sildenafil combined with narcotic-stimulant substances in clubs and entertainment environments cause exaggerated sexual behaviors, which may facilitate the transmission of sexually transmitted diseases. In the present study, opioid, amfetamines, cocaine were detected in ten cases and of these substances, the common one was observed to be tetrahydrocannabinol (THC/marijuana). It was thought that this circumstance may be due to the fact that marijuana is easily accessible. Although there are not much data on the use of PDE-5 inhibitors in combination with drugs, it was considered that there may be a possibility that PDE-5 inhibitors with their synergistic effect may increase the side effects of narcotic substances. In a case presented in England, in a 41 years old patient, inferior MI was developed approximately 12 hours after the combined use of marijuana and sildenafil. The researchers asserted that an interaction exists between marijuana and sildenafil especially through cytochrome P450 3A4 inhibition, and this may have resulted in MI in the healthy individual (18). In another case, a 42-year-old smoker patient had a history of losartan treatment due to hypertension. The patient had experienced atypical chest pain one hour later after having sexual intercourse following cocaine inhalation and sildenafil

use. He had applied to a hospital but died after 12 days, despite treatment. In his autopsy, an intimal tear had been detected in the descending aorta. Although the contribution of cocaine and sildenafil to this condition has yet to be determined, it has been anticipated that vasodilatation caused by sildenafil may disrupt organ perfusion (19).

The frequency and severity of erectile dysfunction increase with age. ED frequency in Turkey has been reported as 69% (mild: 33.2%; moderate: 27.5%; severe: 8.5%) (13). Sildenafil (with a commonly known commercial name, viagra) is currently used by more than 20 million men in more than 110 countries (20). Besides, PDE-5 inhibitors, especially sildenafil, can be added in the formulation of various sexual performance enhancing products and food supplements. Since such products can be easily accessed on the street, in the herbal sellers or via internet, its non-prescribed and uncontrolled use regarding dosage is commonly encountered. Therefore, the possibility of complications that can occur due to these active substances also increases, which creates a public health concern.

CONCLUSION

In our study, over 60% of the cases in which PDE-5 inhibitors were detected in their autopsy were found to have atherosclerotic cardiovascular disease. This suggests that PDE-5 inhibitors may have caused risky cardiac side effects. More studies are needed to be carried out on this subject.

In Turkey, where erectile dysfunction is quite often, studies and training activities aiming to increase the awareness and consciousness level of the society on the subject should be conducted so that the unconscious use of erectile-stimulating drugs outside the physician's control can be prevented. In conclusion, it is considered that the present study will contribute to the literature through revealing the cardiac side effects of PDE-5 inhibitors.

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