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Case Report
Postmortem Toxicology of Tadalafil in a Forensic Case

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ABSTRACT

Tadalafil is an inhibitor of the human enzyme cyclic guanosine monophosphate–specific phosphodiesterase, type 5 (PDE-5). As a mild vasodilator, it is primarily used for the treatment of erectile dysfunction, an increasingly common condition in men. It is also used for treatment of benign prostatic hyperplasia and pulmonary arterial hypertension. Adverse events of this drug are rare. Absolute contraindications include serious cardiac disease. Despite the widespread use of tadalafil, very little is known about its toxicology in forensic pathology and its association with post-mortem redistribution. This study presents a forensic case with possible contribution of tadalafil. The administration of tadalafil might act as a concurrent cause or contributing factor for lethal cardiogenic shock in people with cardiac disease.

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1. Introduction

Tadalafil is an inhibitor of the enzyme cyclic guanosine monophosphate–specific phosphodiesterase, type 5 (PDE-5). It is a mild vasodilator primarily used for the treatment of erectile dysfunction (ED) which is defined as the constant inability to achieve and/or maintain a penile erection sufficient to perform a satisfactory sexual intercourse. The reported prevalence of ED varies from 6% to 64% [1-4]. The identified causes of ED are classified as organic, psychogenic, and mixed causes. Organic causes include vascular, hormonal, neurological, and systemic diseases such as hypogonadism, hyperprolactinaemia, diabetes mellitus, dyslipidemia, and hypertension. Iatrogenic causes are considered organic, and include pharmacological treatments with antipsychotics, antidepressants, diuretics, beta-blockers, and hormones (e.g. prostatic hyperplasia or cancer), surgical treatments such as pelvic surgery, or fractures followed by damage to the pudendal artery or nerve [1, 5-8]. Overall, vascular causes are mainly responsible for organic ED [7, 8], and well-known risk factors for cardiovascular diseases, such as cigarette smoking, alcohol consumption, dyslipidemia, obesity, hypertension, and diabetes mellitus increase the risk of developing ED. Psychogenic causes of ED are often involved in younger patients, and are classified as generalized or situational causes [9, 10]. The ED has a negative impact on patients' self-esteem, with possible repercussions for their daily life, job performance, and social relationships [11].

The diagnosis of ED requires medical history recording and clinical examination, aimed at identifying possible organic or psychological causes, pharmacological therapies or pathologies with a psychological component that may interfere with sexual function [12]. The phosphodiesterase-5 (PDE-5) inhibitors, sildenafil, tadalafil, vardenafil, and avanafil, with different onset of action and duration of effect, induce a natural penile erection by enhancing physiological mechanisms. Alternative treatments, such as intracavernosal and transurethral injections, prosthetic implants or shock waves are used in patients with contraindications to PDE-5 inhibitors to improve penile microcirculation [13-16]. The mechanism of action of tadalafil relies on the selective inhibition of the PDE-5 enzyme in the smooth muscle of corpus cavernosum and in other tissues and organs, such as visceral and vascular smooth muscle, and skeletal muscle. Tadalafil has no effect in the absence of sexual stimulation. when nitric oxide (NO) is released locally following sexual stimulation, the PDE-5 inhibition achieved by tadalafil leads to an increase in cyclic guanosine monophosphate levels of the corpus cavernosum, followed by relaxation of smooth muscle, vasodilatation, and blood flow within the penile tissue, with erection as the final outcome. Tadalafil for PDE-5 is 10,000 times more selective than for PDE-3, and this plays a fundamental role in the safety of this drug. PDE-3 is present in the heart and blood vessels and is involved in cardiac contractility; the poor selectivity of tadalafil for this isoform reduces the risk of relevant harmful effects on cardiovascular function [17]. Following a single 20-mg oral administration, tadalafil is readily absorbed and almost most of it (94%) is bound to plasma proteins. The peak concentration of 378 ng/mL is reached in about 2 hours, but the effects start in 30 minutes and can last for 36 hours [18, 19]. Tadalafil is metabolized by cytochrome P450 3A4 (CYP3A4), has a half-life of 17.5 hours, and its primary metabolite is inactive, mostly eliminated by faeces and, to a lesser extent, by urine [20].

Since 2009, studies on tadalafil with different objectives, such its alternative uses (e.g. in the treatment of severe neonatal pulmonary hypertension), developing and validating procedures for its detection and quantification in biological matrices [21-24], and implementing strategies to uncover tadalafil and unapproved analogues in dietary supplements, counterfeit products, or falsified medicines have been conducted [25, 26]. A recent study discussed the role of tadalafil, along with other PDE-5 inhibitors, as a contributing cause of death in subjects with pre-existing cardiac risk factors or disease [27]. In addition to the conventional use in patients with ED and its safety profile [28, 29], tadalafil can be used for the treatment of benign prostatic hyperplasia, overactive bladder in lower urinary tract symptoms [30, 31] and pulmonary arterial hypertension [32, 33]. Common side effects of tadalafil are caused by vasodilatation in other vascular beds, and include dizziness, headache, flushing, and hypotension, especially in patients treated with nitrates for coronary artery disease, rhinitis, and dyspepsia. Rare, but potentially serious adverse events of tadalafil may include visual impairment or loss, hearing loss, hypotension, cardiovascular disease, and priapism [18, 34]. Despite the widespread use of tadalafil, very little is known about its association with lethal cases in forensic pathology, or related post-mortem toxicology [27, 35].This study aims to present a forensic case with post-mortem toxicology of tadalafil.

2. Case Presentation

In late summer 2014, the body of a 66-year-old man was found sitting on the driver's seat of his car, which was parked inside a rural shed in the countryside near Reggio Emilia (Italy). The body, unclothed, lay supine, and no

evident lesions were observed during investigation at the death scene. Inside the car, both front seats were reclined backwards. A blister pack of 20-mg tadalafil (Cialis®) was found between the front seats, while one-half of tablets were missing. A complete forensic investigation was required by the Public Prosecutor of the local criminal court. The deceased was an Italian man in apparent good health, and the body was at very early stage of putrefaction, with scarce putrefactive fluid trickling from the parted lips. The time of death was unknown and could only be loosely estimated. The medical history was also unknown, and the external examination confirmed the absence of trauma or evident pathology. An autopsy was performed three days after the recovery of the body, and confirmed the absence of trauma. During the autopsy, macroscopic anatomical-pathological findings were detected and recorded and the samples of tissues and organs were collected, fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin (HE) for microscopic observation. Samples of biological fluids (urine, bile, blood of vena cava, and iliac origin) and organs (brain, liver, and kidney) were collected and stored at -20°C for the toxicology assessment.

3. Results

At the autopsy, the deceased subject was reported to have a height of 174 cm and a weight of 75 kg. The macroscopic anatomical-pathological findings, such as massive pulmonary oedema and congestion, cardiac left ventricular hypertrophy (heart weight=520 g) in diffuse myocardial sclerosis, mild arteriosclerosis of the coronary arteries (with approximately 50% stenosis), and advanced atheromatous degeneration of aorta, supported cardiogenic shock as the cause of death. Minor findings included bronchial hyperplasia, hepatic steatosis, and a small surgical scar on the abdomen. The underlying ischemic cardiomyopathy was confirmed by histopathology, which showed disruption of the myocardial cell alignment in myocardial interstitial fibrosis (Figure 1), perivascular myocardial fibrosis with fatty infiltration (Figure 2), as well as massive accumulation of fluid within the alveolar spaces, vascular congestion and thickening of alveolar walls (Figure 3).

The post-mortem toxicology workflow included a preliminary screening of blood by the enzyme-multiplied immunoassay technique (EMIT) for the detection of the most common illicit substances (cocaine/benzoylecgonine, Δ^9-tetrahydrocannabinol-THC, buprenorphine, methadone, amphetamine/ecstasy, benzodiazepines, barbiturates, and opiates). The negative results were confirmed by liquid chromatography with tandem mass spectrometry (LC-MS/MS) performed on the samples of blood, brain and liver. The measurement of blood alcohol by headspace gas chromatography (HS-GC) was also negative, whereas tadalafil was detected in vena cava blood, iliac blood, and urine by LC-MS/MS. The results are shown in Table 1.

4. Discussion

The safety profile of tadalafil, a PDE-5 inhibitor used for the treatment of ED has been confirmed by recent studies [14, 17, 28, 36, 37]. There are no reports of accidental lethal intoxications; only a few cases of sudden cardiac deaths associated with its use and one case of

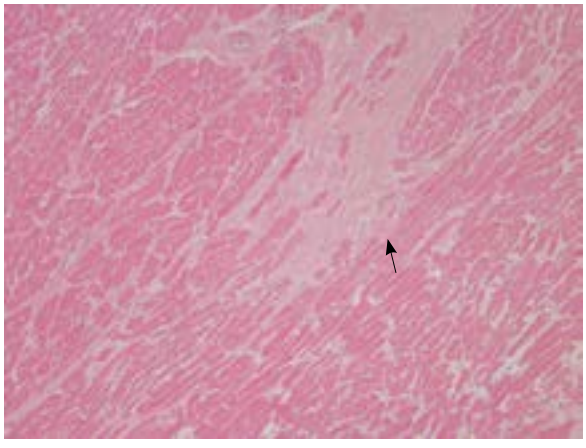

Figure 1. A microscopic image of the heart section showing the bands of pale eosinophilic dense collagen in myocardial interstitial fibrosis (shown by the arrow), in stark contrast with the adjacent vital cardiac muscle cells deeply stained (H&E×200)

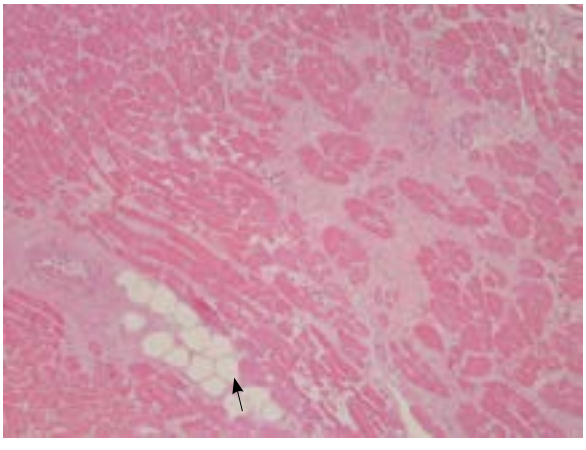

Figure 2. A microscopic image of the heart section showing the bands of palely eosinophilic dense collagen in interstitial and perivascular myocardial fibrosis, with myocardial fatty infiltration (shown by the arrow) (H&E×200)

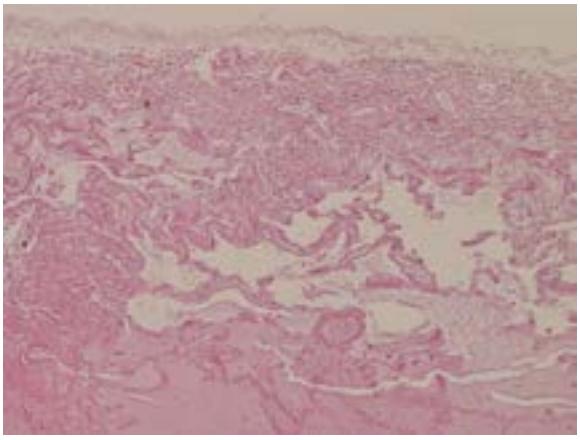

Figure 3. A microscopic image of the lung section showing the massive accumulation of fluid within the alveolar spaces, vascular congestion, and thickening of alveolar walls (H&E×100)

type B aortic dissection [35] have been reported. Rust et al. [21] reported the detection of tadalafil in blood of two forensic cases: A 79-year-old man died after sexual intercourse with a blood concentration of 360 ng/mL (described as "not unusually high"), and a 39-year-old man with a blood concentration of 150 ng/mL (described as "in the therapeutic range") after being charged with rape. Nagasawa et al. [27] reported three forensic cases with post-mortem detection of tadalafil in the cardiac and femoral blood, and suggested that the use of PDE-5 inhibitors may contribute to cardiogenic shock in individuals with pre-existing cardiac disease, "regardless of blood levels". Many studies have highlighted the protective effects of tadalafil against cardiovascular diseases, and its current usage along with analogues for the treatment of neonatal pulmonary hypertension is based on this rationale [32, 33, 38]. In some studies, a crucial protective effect of tadalafil on the cardiovascular system was achieved by diminishing cardiac remodelling [39-42].

The role of tadalafil in forensic medicine remains in the background, with sparse data on therapeutic ranges, toxic/fatal concentrations, and post-mortem toxicology. Several reasons can be postulated for the paucity of data. Firstly, the co-morbidity of ED with coronary artery disease is common [38]. Secondly, when acute or chronic cardiovascular ischemic disease is detected by histological examinations in a natural death, no further contributing causes are usually investigated. Thirdly, routine post-mortem toxicology does not include tadalafil [22]. The absence of a reliable clinical history of the deceased person, as presented in this case study, plays a crucial role in overlooking the post-mortem examination of tadalafil in biological domains. The fact is also reinforced by the reticence with which ED and related treatments are perceived, and thus reported by patients and/or their relatives.

In the reported case study, the presence of a blister pack of tadalafil with missing tablets in the car while the case was not wearing any cloths immediately raised suspicions about the involvement of the drug in the death process. When the post-mortem assessment of tadalafil-was done, the timeline of administration and death could only represent a matter of speculation. Since the reliable data has only been reported on therapeutic concentration of tadalafil in living patients, very little is known about its fatal toxicity and post-mortem toxicology in humans. Curran et al. [19] recommended 10 mg up to 20 mg dose prior to sexual activity, once per day, and reported absolute contraindications, such as serious cardiac disease, recent myocardial infarction or stroke, and uncontrolled blood pressure alterations or arrhythmias.

In the reported case, the blood concentration of tadalafil (4.3-4.8 ng/mL) was very low and within the therapeutic range [21]. However, confounding factors related to the unknown clinical history and the time of death, beside initial putrefaction, did not allow the post-mortem assessment, as well as the reconstruction of the timeline (tadalafil administration and death). Furthermore, the initial dose remains speculative, since the suspect about the excessive self-administration of 30 mg tadalafil was because one-half of 20-mg tablets were missing from the blister pack found at the death scene. Due to the lack of any traumatic event or suspicious evidence, the case

Table 1. Concentration of tadalafil in vena cava blood, iliac blood, and urine detected and quantified by LC-MS/MS

Sample	Tadalafil Concentration
Venous blood (Iliac)	4.8 ng/mL
Venous blood (Cava)	4.3 ng/mL
Urine	8.7 ng/mL

International Journal of
Medical Toxicology & Forensic Medicine

was closed as a natural death case caused by cardiogenic shock in the pre-existing chronic ischemic cardiomyopathy. The authors, however, believe that the administration of tadalafil at a dose higher than 30 mg may had a role as a concurrent cause or indirect contributing factor, as some studies have reported sex-related cardiovascular arrest in mature men at higher cardiovascular risk [43, 44]. For example, the desired effect of tadalafil acted as an intrinsic motivation for sexual activity, which was not supported by cardiovascular conditions of the person. In the literature, the importance of analyzing drugs for the treatment of ED in the post-mortem screening of biological specimens has been emphasized, since cardiovascular risk may be increased by the sexual activity after using such drugs.

5. Conclusions

The presented case supports the potential role of tadalafil in fatal cardiovascular events in people with cardiac diseases. Further studies are needed to investigate the post-mortem toxicology of tadalafil, possibly including PDE-5 inhibitors in routine screening. The aim is to identify a connection between cardiac death and tadalafil administration, and to improve the knowledge of tadalafil toxicity. Furthermore, a study on the post-mortem biochemistry of tadalafil can guide clinicians to improve the management of treatments, for example, in terms of dosage. This confirms once more the benefit of inter-disciplinary cooperation between clinical and forensic practitioners.

Ethical Considerations

Compliance with ethical guidelines

No ethical approval was needed for the present study, since it was requested by a Public Prosecutor of a Criminal Court for a forensic investigation.

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Authors' contributions

Conceptualization: Edda Emanuela Guareschi; Methodology and investigation: All authors; Original draft preparation: Maria Laura Schirripa and Edda Emanuela Guareschi, Resources, review & editing: Edda Emanuela Guareschi and Letizia Gnetti; Supervision, project administration and data curation: Edda Emanuela Guareschi.

Conflict of interest

The authors declared no conflict of interest.

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