

Death Due to Tianeptine Injection Through Inguinal Incision: Two Case Reports İnguinal Kesi Yoluyla Tianeptin Enjeksiyonu Sonucu Ölüm: İki Olgu

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Abstract

In recent years, drug use has come to the forefront as one of the most important problems of public health. Tianeptine is an antidepressant that is structurally similar to tricyclic antidepressants and is used for the treatment of depression but is also abused because its pleasing feature has been recognized by drug users. Two forensic cases were autopsied with an interval of 25 days. One case had unilateral unusual inguinal lesions. The other case bilateral unusual inguinal lesions. It was understood that these lesions were performed, improved surgical catheter incisions in order to facilitate intravenous injections for drug abuse. This application, which was detected in the inguinal region, was found to be interesting. It is aimed to raise the awareness of this application, which is not found in the literature. As a result of the intense human transit, substance abuse habits and methods have also been transferred to citizens of the other countries, and new applications have emerged.

Keywords: Tianeptine; Autopsy; Inguinal Incision; Injection

Özet

Madde kullanımı son yıllarda halk sağlığının en önemli sorunlarından biri olarak ön plana çıkmaktadır. Tianeptin, trisiklik antidepressanlara yapısal olarak benzerlik gösteren ve depresyon tedavisi amacıyla kullanılan, ancak kullanıcılar tarafından keyif verici özelliğinin tespit edilmesi sonucu kötüye kullanımı da olan bir antidepressandır. Yirmi beş gün arayla otopsi gerçekteşen adli nitelikli iki olgudan birinde tek taraflı, diğerinde ise iki taraflı inguinal sıra dışı lezyonlar saptandı. Bu lezyonların ilaç kötüye kullanımı amacıyla yapılacak intravenöz enjeksiyonları kolaylaştırmak amacıyla daha önceden oluşturulan, iyileşmiş cerrahi katater insizyonları olduğu anlaşıldı. İnguinal bölgede saptanan bu uygulama ilginç bulunmuş ve literatürde rastlanmayan bu tianeptin uygulamasının farkındalık oluşturma-sı amaçlanmıştır.

Anahtar Kelimeler: Tianeptin; Otopsi; İnguinal İnsizyon; Enjeksiyon

1. Introduction

Drug abuse is steadily increasing around the world despite the adoption of various measures and has come to the forefront as one of the most important problems of public health. According to the 2017 European Drug Report, published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), herbal cannabinoids, heroin, cannabinoid resins, amphetamine and cocaine are among the top five drugs that are abused commonly (1).

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Tianeptine is an atypical antidepressant that is structurally similar to tricyclic antidepressants, and is used for the treatment of depression. However, it is also abused by drug users (2,3). Gassaway et al (4) reported that tianeptine is an efficacious μ -opioid receptor (MOR) and δ -opioid receptor (DOR) agonist, and they proposed that MOR-agonism (or combined MOR/DOR-agonism) underlies the clinical, preclinical and in vitro effects of tianeptine. Therefore as an atypical antidepressant and neurorestorative agent and μ -opioid receptor agonist, it is abused especially by heroine addicts in case of the lack of heroine.

It was found that 37.5mg tianeptine has the equivalent anxiolytic effect of 20 mg fluoxetine (5,6). In addition, it has antidepressant effects through the glutamatergic sys-

tem (7). This effect of tianeptine through glutamate may play a role in its psychostimulant effect and hence in its addictive effect (8).

Tianeptine is metabolized in the liver without the use of the cytochrome P450 system. It does not undergo the first-pass metabolism, and 8% is excreted unchanged by the kidneys. When taken with alcohol, its absorption and plasma levels are reduced. Its half-life is 2.5 hours (9). The administration of high doses of tianeptine in mice has been reported to temporarily affect nerve cells without significant stimulatory effect, to stimulate muscle activity and to reduce the duration of sleep. It has also been noted that tianeptine enhances attention and learning in terms of cognitive performance (10). Tianeptine is sold as 12.5 mg tablets in the market. Although the most effective therapeutic dose is 37.5 mg daily, it may be given up to 3000 mg (3). The risk of toxicity is low. For example, when a single dose of 337.5 mg is given, only temporary nausea, vomiting and sedation are observed. No toxic effect was observed even in a case receiving 1875 mg/day for 7 months (9). It was reported that long-term tianeptine use had no effect on cognitive function, psychomotor activity, cardiovascular system, sleep and weight. In several studies conducted before, it was reported that the most common side effects observed during initial phase were nausea, vomiting, constipation, abdominal pain, headache, dizziness and sleep disturbance. It was also determined in previous studies that as the treatment progressed, these effects decreased and the tendency to abuse was low (11). The dose is increased over time because of the recognition of the pleasing feature of the substance. However, since it can be well tolerated despite increasing dose, the likelihood of abuse is also increased. Ventricular extrasystole, hyper/hypotension and coma can be observed in severe intoxications (12).

Tianeptine is also used intravenously (IV) although it is produced in tablet form. IV drug users crush the tablets and often dissolve in tap water to prepare the solution. The solution damages the vessels and causes thrombus formation in the vessels. The thrombus creates a suitable environment for microorganisms and triggers the infection process. Complications usually develop 6 months after drug use but sometimes may be seen earlier (13). İlhan et. al. (14) reported that femoral artery pseudoaneurysm developed in a case receiving IV tianeptine.

Two cases occurred with an interval of 25 days in the same district. These cases, who died due to tianeptine intoxication, were autopsied by Trabzon Group Management of Turkish Council of Forensic Medicine. Improved surgical incisions, which were thought to be pre-formed in order to facilitate IV injections into the femoral vein in

the inguinal region, were detected in autopsies. This application was found to be interesting in terms of the route of administration in drug abuse. The aim of our study was to discuss two cases that seemed to die of tianeptine intoxication due to an unusual application.

2. Cases

Case 1: A 51-year-old male was found lying dead in a hotel room. The hotel room was not cluttered, and it was seen that there were injectors beside the bed. The case was autopsied one day later.

External examination findings: It was a male dead body measured as 170 cm in length and 80-85 kg in weight. There was an old scar tissue measuring 5x5 cm in the left lower quadrant of the abdomen and 12 cm in the left inguinal region. There was a regular, epithelialized, non-purulent open wound, measuring 1.5x0.3 cm in the left inguinal region. There was a rigid subcutaneous mass measuring 2 cm in the right inguinal region. There was edema in both legs. It was observed that there were petechial hemorrhages on the front sides of both legs and ecchymoses in different colors in both antecubital regions (Fig 1).



Fig 1. Ecchymoses due to injection in different colors in antecubital region.

Internal examination findings: There was edema in the brain and lungs and also inside the tracheal lumen. There was an atherosclerotic plaque that narrowed the vessel lumen by 10-20% in the coronary arteries. It was observed that femoral artery and vein were located just below the wound on the left inguinal region and that the depth of the open wound extended to the subcutaneous fascia and measured 2 cm.

Chemical analysis findings: Analysis was performed using femoral blood samples on the AB SCIEX LC/MS/MS 5500 device. This analysis revealed that tianeptine

was 4401 ng/ml, citalopram was 11 ng/ml, piroxicam was 288 ng/ml and 7-aminoclonazepam was below the detection level (< 1 ng). The presence of the same substances in urine was confirmed.

Histopathological examination findings: Granulomatous inflammation foci and focal necrotic foci were diffusely observed in the lungs as a foreign body. It was detected that there were foreign bodies showing reflection in polarized light in these foci (Fig 2), chronic inflammation in the liver, and mild perivascular fibrosis in the heart.

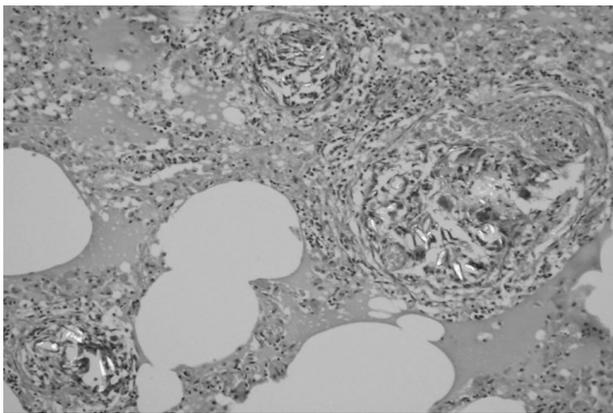


Fig 2. Foreign bodies showing reflection in polarized light in granulomatous foci in the lung.

Case 2: A 38-year-old male suddenly fainted and died in the kitchen of his workplace. It was found that there were injectors on the refrigerator in the kitchen. He had tianeptine tablets in his pockets. He had a history of drug abuse for 15 years. It was stated that he dissolved tianeptine tablet in water and injected it into a vein when he did not find any drugs, and he was treated for substance abuse (tianeptine, heroin) and depression one week before his death. The case was autopsied one day later.

External examination findings: It was a male dead body measured as 168 cm in length and 70-75 kg in weight. There were 2 old and 1 new needle traces in the right antecubital region. There were 3 old needle traces in the left antecubital region. There were retracted and rigid surgical wounds on left and right inguinal regions consistent with the femoral artery and vein traces measuring about 0.5 cm in depth and 1 cm in diameter including with a 2x1 cm scar tissue at its lower end. There were numerous ecchymoses in millimeter size, purple color on the inside of the right thigh and on both legs and 2 needle traces showing mild ecchymosis around the left wrist.

Internal examination findings: There was edema in the brain and lungs as well as inside the tracheal lumen. There was an atherosclerotic plaque that narrowed the

vessel lumen by 80% in the coronary arteries. It was observed that the depth of the wound in both inguinal regions extended to the fascia where the femoral artery and vein were covered and there was ecchymosis in the surrounding soft tissues.

Chemical analysis findings: Analysis was performed using femoral blood samples on the AB SCIEX LC/MS/MS 5500 and AGILENT 1200 HPLC devices. This analysis revealed that tianeptine was 538 ng/ml, and nordiazepam was below the detection level (<1 ng). Tianeptine was detected in bloody injectors and “Stablon” inscribed on tablets were obtained from the crime scene by the SHIMADZU GC/MS and AB SCIEX LC/MS/MS 5500 devices.

Histopathological examination findings: It was observed that there were diffuse granulomatous inflammation foci as a foreign body in the lungs and chronic inflammation in the liver. There was an atherosclerotic plaque that narrowed the vessel lumen by 80% in the coronary arteries. On the skin samples obtained from the inguinal region, there were multiple granulomatous inflammation foci as a foreign body in the deep dermis and perivascular and interstitial mixed cell infiltrate in the superficial and deep dermis. There were also fresh bleeding and hemorrhagic abscess foci. It was observed that there were foreign bodies showing reflection in polarized light in the granulomatous foci of the lung and the skin (Fig 3).

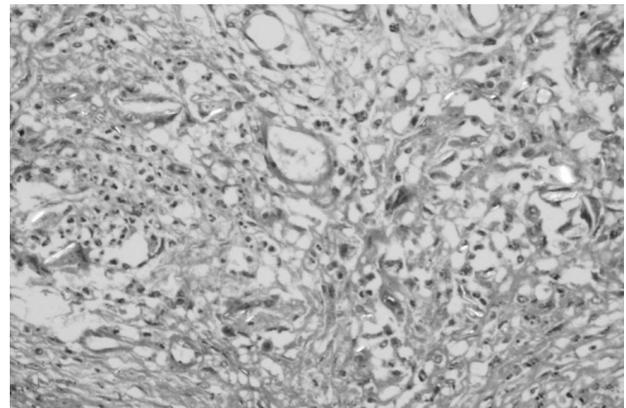


Fig 3. Deposites of foreign substances showing reflection in polarized light in the skin.

3. Results and Discussions

In recent years, studies have been conducted to reflect the causes of tianeptine abuse or dependence because just as one of our case, it is a μ -opioid receptor agonist and abused by heroin addicts. Additionally unusual preparatory incision is also unique.

In a study of Ferreira et al. (15) they identified a 40-year-old woman who had a history of alcohol depend-

ence and consumed about 10 coffees and 40 cigarettes a day. The patient said that she used tianeptine for many years and was admitted to a psychiatric ward 3 times in the last 6 months because they used a higher dose (1286 mg per day). She also stated that she needed to consume more drugs since it is a stimulant drug and increases physical energy. One of our cases had previously received heroin addiction treatment. Citalopram, piroxicam, 7-aminoclonazepam and nordiazepam in addition to tianeptine were detected in both of our cases.

In another study, 24 volunteer male patients with opiate addiction, who had a history of tianeptine abuse, were kept under clinical observation. In the patients aged between 21 and 33, the mean duration of tianeptine use was 5 months and the mean daily dose was 40 tablets. This is equivalent to an average of 500 mg for IV injection. The patients used tianeptine in combination with some antihistaminic agents (16). In another case report, a 26-year-old man was found dead in his bed and had foam mushrooms around his mouth. There were an empty tianeptine package and a suicide note near the dead body. Tianeptine was detected in toxicological samples, and ethanol was found in femoral blood samples (12). Ethanol was not detected in both of our cases, but there were injectors containing tianeptine in the places where they died, and they had tianeptine tablets in their pockets.

Tianeptine, which is less addictive than benzodiazepines and opiate analgesics, has been sold for a period of time without prescription in Turkey. However, when addictions and deaths emerged, they were included in the green prescription in 2012 in Turkey. Therefore, tianeptine is still available illegally in Turkey except medical prescriptions.

Trabzon, where the autopsies were performed, is 188 km from the border of Georgia and is a reference center for the region. It is already known that this drug is purchased in large quantities by some Georgians in Turkey. For this reason, it is called «Georgian drug» in this region (17). This drug, which is sold in tablet form, is designed for oral use. Tianeptine, which has been started to be used for the treatment of depression, is also abused since it has low intoxication potential, good tolerance, and pleasing effects. Patients can receive very high tianeptine doses, especially for oral use because it can be well tolerated. Tianeptine was detected as 4401 ng/ml and 538 ng/ml in the femoral blood samples of our cases. According to these blood level measurements, the second case might not die due to tianeptine intoxication. Besides, when the second case was considered, apart from atherosclerosis (80% occlusion), another reason for death except tianeptine intoxication was not considered to be logical.

The Sarp land border gate between Georgia and Turkey was opened in 1988, and Georgia and Turkey both relaxed visa requirements for Georgian and Turkish nationals in 2011. Thus, mutual commercial and touristic relations between the citizens of the two countries are increasing day by day. This situation, which allows passing through the border only with the identity card, has naturally led to some cultural and social consequences. This drug is known to be abused orally in general. Another type of usage, which is intravenous injection after dissolving in warm water, seems to be widely preferred in Georgia and the surrounding region (16). Both of our cases were registered in Hopa, which is located on the border of Georgia, and they lived in the same region. Since Hopa district has this geographical position, it is known that people living in this district are engaged in intensive social interaction with the Georgian society. Naturally, it can be expected that people in this region use similar routes of administration for tianeptine abuse. As a result of the intense human transit, substance abuse habits and methods have also been transferred to citizens of the other countries, and new applications have emerged. We think that both of these two cases tried this administration method, which is new for Turkey, as a result of this interaction.

Cases of intravenous drug abuse through the intact skin tissue are seen in Turkey. In one case, bilateral pseudoaneurysm developed secondarily to the use of tianeptine. Unlike our cases, the administration in this patient, which did not result in death, was performed directly intravascularly through the intact skin tissue (14). There were cases of intravenous drug injections in literature (18-20), as in our cases, we did not find a presence of preparatory incision in the literature that would make the femoral vein, which is selected as an application region, visible. Tianeptine, which is made soluble, has to be given by venous route. If the injection is performed in intra-arterial route, thrombus and infection may develop in the arterioles. Gangrene develops rapidly in such cases (13). We believe that preparatory incisions in our cases made the femoral vein visible and thus these incisions may be planned to avoid possible adverse outcomes of intra-arterial injection.

After autopsy incision was performed in the inguinal region, it was observed that there were macroscopic and microscopic findings suggesting chronic use together with a large number of fresh injection traces around the femoral vein. Although no similar findings are found in the literature, both of our cases had smooth-edged surgical catheter incisions that were created surgically on traces of the femoral artery and vein in the inguinal re-

gion and completed their own recovery processes (Fig 4). First of all, it was thought that these wounds may be due to the granulation tissue formed by repeated injections to the same region. The reason to prefer inguinal region for incision was thought to be the aim of hiding the incision trace. It was thought that these incisions, which were understood to be very well calculated topographically, were considered to be probably performed by a health worker with an advanced knowledge of anatomy. The edges of these incisions, which were unilateral in the first case and bilateral in the second case, were blunt and also no infection was observed. It was observed that there were wounds, which were incised in the presence of fascia on the femoral artery and vein and completed their own recovery processes. The femoral vein was reached directly in vertical initiatives to these areas with injector during



Fig 4. Smooth-edged surgical catheter incisions..



Fig 5. The femoral vein was reached directly in vertical to these areas with injector initiatives.

the autopsy and venous blood was drawn into a syringe (Fig 5).

Both cases had no chance of treatment and were found dead. However, it is also possible that such intoxication cases receive an immediate intervention. In such patients with tianeptine abuse admitted to the emergency departments, injection traces were detected in the extremities (14,17). In accordance with the literature, new and old injection traces and small subcutaneous bleeding sites on the traces of vessels were observed in the extremities of both cases.

4. Conclusion

Health personnel, especially those working in emergency departments, should be cautious about patients having a similar finding in the inguinal region with or without a known substance use. It would be useful to analyze this finding in terms of substance dependence. Moreover, care must be taken against possible new applications that are not yet included in the literature. As in our cases, no literature information has been obtained about an unusual preparatory incision for injection.

Both cases presented in this study were considered to die due to possible tianeptine intoxication. Despite the fact that it serves a very wide geographical area and a crowded population, Trabzon Group Management of Turkish Council of Forensic Medicine did not observe any similar cases in the following 4 years after these two consecutive autopsy cases and in the 6 years before this incident (2007-2016). Therefore, we believe that it is useful that clinicians and forensic specialists carefully evaluate such suspicious findings in these types of cases, which are not often encountered in autopsy practice.

Conflict of interest

The authors declare that they have no conflict of interest.

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