Farmakoterapia w psychiatrii i neurologii, 2014, 1, 37–42

Praca kazuistyczna

Case report

Ewa Dopierała, Ewa Ferensztajn, Janusz Rybakowski

Dependence on tianeptine: case report and review of the literature

*Uzależnienie od tianeptyny: opis przypadku i przegląd piśmiennictwa**

Klinika Psychiatrii Dorosłych, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu

ABSTRACT

Tianeptine is an atypical tricyclic antidepressant, the efficacy of which in the treatment of depressive episodes, dysthymia, adjustment disorder, and anxiety is comparable with the selective serotonin reuptake inhibitors (SSRI). The main mechanism of tianeptine's action is based on the modulation of stress axis activity and increase of serotonin reuptake with additional pro-dopaminergic effects. Despite the many advantages, we find more and more reported cases of addiction to tianeptine, due to its psychostimulant properties and lack of side effects. It is reported in the literature that the dependence index (the so-called DSI – doctor shopping index) for tianeptine is at a level similar to benzodiazepines. We present the case of a 43 year-old woman with bipolar disorder and multiple drug abuse, who took tianeptine up to the dosage of 1125 mg/day (90 tablets). Treatment with valproic acid, bupropion and sertraline resulted in a gradual improvement of her mental condition, enabling her to function satisfactorily day to day.

STRESZCZENIE

Tianeptyna to atypowy trójcykliczny lek przeciwdepresyjny. W leczeniu epizodów depresji, dystymii, zaburzeń adaptacyjnych i lękowych jego skuteczność jest porównywalna do leków z grupy selektywnych inhibitorów wychwytu zwrotnego serotoniny (SSRI). Główny mechanizm działania tianeptyny opiera się na regulacji aktywności osi stresowej i nasileniu wychwytu zwrotnego serotoniny, z dodatkowym działaniem prodopaminergicznym. Mimo wielu zalet pojawia się coraz więcej doniesień o przypadkach uzależnienia od tianeptyny, ze szczególnym zwróceniem uwagi na jej właściwości psychostymulujące, przy braku działań niepożądanych. W literaturze opisuje się, iż wskaźnik uzależnienia, tzw. DSI (*doctor shopping index*), dla tianeptyny lokuje się na poziomie podobnym do benzodiazepin. Przedstawiamy przypadek 43-letniej pacjentki z chorobą afektywną dwubiegunową i uzależnieniem mieszanym, przyjmującej dawki 1125mg (90 tabletek) tianeptyny na dobę. W wyniku leczenia kwasem walproinowym, bupropionem i sertraliną, uzyskano stopniową poprawę stanu psychicznego, umożliwiającą zadowalające codzienne funkcjonowanie pacjentki.

Key words: addiction, bipolar affective illness, tianeptine

Słowa kluczowe: uzależnienie, choroba afektywna dwubiegunowa, tianeptyna

INTRODUCTION

Tianeptine is a new generation tricyclic antidepressant, introduced in Europe in the 1990s. The basic mechanism of its action is connected with modulation of the stress axis activity (LHPA limbic-hypothalamic-pituitary-adrenal axis) (Delbende et al., 1994), the hyperactivity of which has often been discussed in the context of depressive disorders (Twardowska and Rybakowski, 1996). A reduction in the activity

* Artykuł w języku polskim jest dostępny w wersji elektronicznej (fpn.ipin.edu.pl).

of the LHPA axis may prevent the adverse structural changes in the hippocampus that occur under stress (Holsboer and Barden, 1996) by regulating the processes of neuronal plasticity, stimulation of neurogenesis and reduction of neuronal apoptosis and atrophy (Magarinos et al., 1999, Kasper and McEwen 2008).

Unlike most antidepressants, which are selective serotonin reuptake inhibitors (SSRIs), tianeptine intensifies the neurotransmitter re-uptake and reduces its amount in the synaptic space (Datla and Curzon 1993). In addition to this it has a unique mechanism of action on the glutamatergic system, involving a blockage of the NMDA receptors (Kole et al., 2002) and the reduction of excessive glutamate concentrations, especially in the hippocampus and cerebral cortex (Reagan et al., 2007, Svenningsson et al., 2007). Additional mechanisms of action involve an indirect influence on the adrenergic system, and the inhibition of excessive cholinergic activity and prodopaminergic action. The latter mechanism may explain tianeptine's clinical efficacy in the treatment of depressive disorders in patients with alcohol dependence (Habrat and Załoga 2006) and its beneficial effects on sexual functions.

It has been shown that the antidepressant and anxiolytic efficacy of tianeptine is similar to the efficacy of the selective serotonin reuptake inhibitors (SSRIs) (Kasper and Olie 2002, Novotny and Faltus 2002). Its clinical effectiveness in the treatment of depressive episodes, mainly mild or moderately severe, but also heavy and drug-resistant (Tobe and Rybakowski 2013), has been assessed repeatedly. The drug is also effective in the treatment of dysthymia, adjustment disorder (Brink et al., 2006) and somatic symptoms of anxiety, particularly in the gastrointestinal tract. It has been also demonstrated that tianeptine is effective and well-tolerated by patients who are particularly vulnerable to the adverse effects of medication i.e. the elderly or patients dependent on alcohol (Vukovic et al., 2009). Good efficacy is associated with good toleration of the drug, absence of excessive sedation or weight gain, sexual dysfunction or problems with the cardiovascular system. Tianeptine is metabolised in the liver without cytochrome P450, which reduces the risk of its interaction with other psychotropic drugs.

Contraindications to the use of tianeptine include hypersensitivity to the drug, age below 15, and its combination with non-selective MAOIs. In spite of the fact that the product leaflet includes information about rare adverse effects in the form of dependence or abuse of tianeptine, little is still known of these phenomena.

One of the indirect indicators of the addictive properties of medication, reached by means of statistical and financial data analysis, is the so-called "doctor shopping" which involves patients visiting a number of doctors simultaneously in order to get prescription drugs. The Doctor Shopping Index (DSI) is calculated on the basis of two values: the amount of the drug obtained following recommendations and by additional means of "doctor shopping". DSI is defined as a percentage relation between the two values mentioned above. It has been shown that the DSI for the addictive potential of tianeptine is on a par with benzodiazepines (Rouby et al., 2012).

The DSI for tianeptine is 2%, which is the highest among other investigated antidepressants such as mianserin, mirtazapine, venlafaxine, amitriptyline and milnacipran, which scored from 0.4% to 1%. Flunitrazepam (withdrawn in Poland in 2006) had the highest DSI (30.2%), while the DSI values for other benzodiazepines (clonazepam, zolpidem, oxazepam, diazepam, bromazepam) ranged from 2.0% to 3.0%. The DSI for tianeptine suggests that it may be abused.

Despite the many advantages and encouraging research results, more and more cases of tianeptine dependence are being reported (Leterme et al., 2003), including the case, presented below, of a patient with tianeptine dependence syndrome.

CASE STUDY

A female patient, aged 43, presented herself at the admissions department of the Adult Psychiatry Clinic in December 2013 complaining of severe depressive symptoms, associated with suicidal thoughts and an inability to stop taking large doses of tianeptine and clonazepam. The patient was then hospitalized for the second time in her life, with a diagnosis of a depressive episode in bipolar disorder and mixed dependence. The examination of her mental condition on admission revealed depressed mood and lower psychomotor performance, tearfulness, irritability, inner restlessness, features of anxiety in speech and shaking hands, guilt, resignation and suicidal thoughts, insomnia and lack of appetite. No delusions, disorders of perception, attention or memory were noted at the time.

Physical examination revealed that the patient was underweight (BMI 17.9). She had pale skin and mucous membranes, her thyroid gland was enlarged (thyroid nodules revealed in an interview); there was a scar on the left side of her ribcage, formed as a result of the closure of ductus arteriosus surgery at 4

years of age. In an interview the patient also reported menometrorrhagia. Laboratory tests showed considerable anaemia and iron deficiency. The results of other laboratory tests were within the norms.

The patient was unmarried, with higher education (a degree in pedagogy). She was professionally active as a primary school teacher in grades one to three; she was artistically talented (graduated from secondary art school) and single, with one 8-year heterosexual relationship revealed in her life though she never had sexual relations. In adolescence she suffered from episodes of anorexia nervosa, abused laxatives and weighed 48kg (BMI = 16). At the time of admission she lived with her mother and brother, who was diagnosed with alcohol dependence. Depressive disorders and suicide occurred in her father's family.

The patient's first experiences of mood disorders occurred in 2006, after her father had been diagnosed with cancer. The patient's condition gradually deteriorated from that time; she experienced sadness, depression, irritability, lack of energy and feelings of resignation which significantly disrupted her daily functioning. In March 2007, she saw a psychiatrist who diagnosed her with adjustment and anxiety disorders. He recommended treatment with paroxetine, buspirone and clonazepam, and consequently the patient was on sick leave for a year. After her father's death in October 2007 the patient chose to discontinue paroxetine and buspirone, and increased her daily intake of clonazepam to 2.5 mg a day.

Her mental condition deteriorated, with considerable emotional lability, excessive crying, constant fear, anxiety, a strong sense of guilt, and suicidal thoughts, resignation, ocassionally higher psychomotor performance, and aggression. Due to the severity of symptoms and the abuse of clonazepam, the patient was admitted to emergency, initially without consent, to the Adult Psychiatry Clinic in Poznan, where she was diagnosed with mixed episodes in bipolar II disorder. As a result of applied psychofarmacotherapy, the patient's condition was rapidly improved. Three weeks later she was discharged with a prescription for valproic acid at a dose of 1200mg per day, and a recommendation for follow-up treatment at the Outpatient Mental Health Clinic.

A month later the patient's mental condition had deteriorated, as fear, anxiety, worry and lack of energy surfaced again. She was additionally prescribed 0.5 mg of clonazepam and tianeptine, initially at 12.5mg, twice a day. After 2 months, the patient chose to discontinue valproic acid, but her dose of tianeptine was increased to 37.5 mg/d. Consequently, she took clonazepam and tianeptine in the recommended doses for about four years. During that time she experienced some periods of depressed mood, anxiety, lack of energy and motivation, difficulty getting out of bed in the morning, and moderately intense withdrawal from social life, which lasted for more than two weeks. The patient also reported some periods of hypomanic symptoms of irritable mood, increased activity, spending large sums of money without any significant purpose and a reduced need for sleep. Mood disorders resolved without modification of the pharmacological treatment, but with greatly disrupted functioning. During that period the patient took a second year-long sick leave from work.

At the turn of November/December 2012 she began to self- modify the medication dosages; over a few month months she gradually but regularly increased the amount of tianeptine, arriving at 90 tablets/day (total 1125mg) in October 2013, and 15 tablets of 0.5 mg clonazepam (7.5 mg) daily. She obtained prescriptions from several doctors simultaneously, but gaining access to such a large quantity of drugs soon caused her financial problems. Her main motivation for taking tianeptine was the desire to improve the way she felt, which she interpreted as the disappearance of depressive symptoms, especially fatigue, depression and anxiety. She expected that she would function better professionally, as her performance of social roles worsened with increased depressive symptoms. She said that she took the drug "like candy" as it made her feel "better and stronger". However, every time she took the drug the effect was only short-lived, which encouraged her to gradually increase the doses throughout the day. Despite taking large doses of drugs, over the last three months prior to her admission she almost never left her room, except to go to work; she had trouble getting up in the morning, smoked a lot of cigarettes, had no appetite, and lost approximately 8kg.

Since admission, the patient presented the symptoms characteristic of a major depressive episode without psychotic symptoms. Tianeptine and clonazepam were discontinued and substituted with valproic acid, at an initial dose of 1000 mg/day, quetiapine 100mg/night, iron chloride at 105mg 2x/d due to the anaemia. There were withdrawal symptoms such as nausea, trembling hands, feelings of excessive muscle tension, especially in the throat area, difficulty swallowing, muscle pains, transient feelings of cold, buzzing noise in the ears, excessive sweating, blurred vision, dizziness.

A test for valproate concentrations in the blood showed a concentration of 2 mg/ml as the patient admitted that she was not taking the drug while in the ward. It turned out that the patient had tianeptine and clonazepam on her but the urine tests for the presence of BZD was negative. A new routine was then started; the patient's drug-taking was monitored and the concentration of valproic acid in the serum regularly checked. The dose of valproic acid was increased to 1500 mg/d; it was combined with 150mg bupropion a day, increased after 2 weeks to 300mg/d.

The patient's condition gradually improved, with better mood, improved sleep and performance and disappearance of suicidal thoughts, but with lingering resignation, guilt and low self-esteem. Withdrawal and anxiety in dealing with others still continued, as did the fear of coping with daily duties after returning home and to work. The treatment was modified with sertraline, the dose being gradually increased to 150 mg/d, while the dose of bupropion was reduced to 150 mg/d. The patient's lab tests results improved. After five weeks in the ward, she had gained 6kg; she began to take part in gymnastic exercises and occupational therapy. Due to considerable anaemia and irregular, heavy periods, she underwent gynaecological consultation, which revealed uterine leiomyomas, and surgery was recommended.

Psychological tests revealed an average intelligence of IQ=97, lower than average working memory and short-term (auditory) memory capacity also lower than average, ability to focus attention and good psychomotor performance. It is likely that the results of the tests of cognitive functions were affected by long-term abuse of tianeptine and benzodiazepines, periodically combined with alcohol.

The patient's condition kept improving with better mood and performance and decreased fear and anxiety. She began planning her return to work, renewal of social life, and declared that she would undergo gynaecological treatment. She also began sketching with charcoal, which is what she used to do but had given up a few years before, yet she continued to express fears that she might not be able to resist her addiction in the future.

DISCUSSION

There are many similar descriptions of tianeptine dependence/abuse in the literature, which highlight its good psychostimulating properties, good tolerance and low toxicity at doses ten times higher than recommended. Typical clinical characteristics of tianeptine dependent patients include a strong desire to ingest the drug, annoying withdrawal symptoms, ineffective attempts to stop taking it, development of drug tolerance, reduced interests, and increased amount of time needed to obtain the drug with all its social, professional and financial impairments. There are often other previous drug or alcohol dependencies/abuse present in the patient's history, along with personality disorders or presence of affective illnesses in the family history.

Kisa et al., (2007) describe the case of a 34-year-old patient receiving tianeptine at 750mg a day for a year, with good tolerance. Initially, the drug yielded a positive effect at a dose of 37.5 mg/d in monotherapy treatment of post-traumatic stress disorder, which was continued for a year. With the deterioration of her mental condition after the birth of her son, the patient began to gradually increase the dose of tianeptine, without adverse reactions. The patient felt better and stronger, but the depressive symptoms progressed, with a simultaneous 15kg loss of body weight. Her repeated attempts to discontinue the drug proved ineffective, and soon the financial consequences of the addiction ensued. After discontinuation of tianeptine and its substitution with venlafaxine, a number of withdrawal symptoms appeared, including a strong desire to ingest the drug, nausea, burning sensations and tingling all over the body, insomnia and tearfulness, which resolved within a week. The patient was discharged in a balanced mental state with a recommendation to take venlafaxine at a dose of 150mg/d.

Vandel et al., (1999) describe the case of a 30-year-old woman treated for depression three times with tianeptine at 12.5mg. The patient increased her doses spontaneously, reaching the level of 150 tablets a day with a psychostimulating effect. No adverse effects were noted at all at such high doses of the drug and the liver parameters were correct. After seven months of taking the drug, the patient reported for detoxification treatment. She suffered from withdrawal symptoms including muscular pains and feeling cold, which were treated with phenothiazine and tetrazepam.

Saatçioğlu et al., (2006) presented the case of a 24-year-old man using tianeptine in doses up to 3000mg a day for a year, with very good tolerance and liver function parameters. An earlier interview revealed a dependence on cannabinoids, opiates and cocaine. Leterme et al., (2006) presented five cases of the use of tianeptine at doses higher than recommended, in combination with other psychotropic drugs. Discontinuation of tianeptine was difficult,

with the presence of anxiety and other disorders, resulting in most patients becoming re-addicted.

A probable mechanism of tianeptine dependence is based on its dopaminergic properties. In animal model studies, it has been demonstrated that the drug increases the release of dopamine in the nucleus accumbens, and in higher doses also in the frontal cortex (Sacchetti et al., 1993), which causes psychomotor agitation (Vaugeois et al., 1999). The dysregulation of the dopaminergic system is also indicated by a case report of tianeptine causing extrapyramidal symptoms (Lamouchi et al., 2004). Dependent on the dose, the drug blocks an increase in the stress-induced concentration of noradrenaline in the frontal cortexes of rats (Sacchetti et al., 1993).

In the case described in this paper, the anti-depressant treatment with bupropion and sertraline focused on increasing the dopaminergic effect, so as to replace the earlier effect of tianeptine. Also quetiapine, in addition to its mood-stabilizing effect, indirectly increases levels of dopamine in the prefrontal cortex.

The phenomenon of addiction to tianeptine is particularly pronounced among former opiate abusers (Vadachkoria et al., 2009) and people previously dependent on other psychoactive substances (Guillem and Lépine 2003), who are mostly younger, under the age of 50. A correlation between the effects of tianeptine and morphine has been discussed in recent years. Chu et al. (2010) demonstrated, in an animal model, the effectiveness of tianeptine administered in combination with morphine in the reduction of the morphine analgesic tolerance development and lowering the incidence of naloxone withdrawal symptoms. They concluded that tianeptine can be a substance effectively inhibiting physical dependence on morphine and its use may be beneficial in long-term pain management. Puig et al., (1993) argued that comedication of tianeptine with morphine affects the metabolism of serotonin receptor (5-HT) at the level of the spinal cord, through an increase in the amount of 5-hydroxyindole in the area.

It should be emphasized that tianeptine resembles, in its structure and psychotropic profile, its predecessor - amineptine (traded as Serveron), which was withdrawn from the market in 1999 because of its addictive properties. Tianeptine is not available in the United States, Canada, UK, Australia and New Zealand. Because of these addictive properties the drug's product leaflets have included a warning since 2007, and in France it has been controlled similarly to narcotic drug since 2012.

The case described in this paper is probably the first Polish report on tianeptine dependence. We wished to focus the attention on the risks connected to the addictive potential of tianeptine, which is commonly regarded as harmless and safe.

BIBLIOGRAPHY

1. Brink CB, Harvey BH, Brand L. Tianeptine: a novel atypical antidepressant that may provide new insights into the biomolecular basis of depression. Recent Pat CNS Drug Discov. 2006; 1: 29-41.
2. Chu CC, Shieh JP, Shui HA, Chen JY, Hsing CH, Tzeng JI et al., Tianeptine reduces morphine antinociceptive tolerance and physical dependence. Behav Pharmacol. 2010; 21: 523-529.
3. Datla KP, Curzon G. Behavioural and neurochemical evidence for the decrease of brain extracellular 5-HT by the antidepressant drug tianeptine. Neuropharmacology. 1993; 32: 839-845.
4. Delbende C, Tranchand Bunel D, Tarozzo G, Grino M, Oliver C, Mocaër E et al., Effect of chronic treatment with the antidepressant tianeptine on the hypothalamo-pituitary-adrenal axis. Eur J Pharmacol. 1994; 251: 245-251.
5. Guillem E, Lépine JP. Does addiction to antidepressants exist? About a case of one addiction to tianeptine]. Encephale. 2003; 29: 456-459.
6. Habrat B, Załoga B. Skuteczność i tolerancja tianeptyny w leczeniu zaburzeń depresyjnych u pacjentów uzależnionych od alkoholu. Wieloośrodkowe badanie kontrolowane metodą podwójnie ślepej próby z użyciem fluwoksaminy. Psychiatr Pol. 2006; 40: 579-597.
7. Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev. 1996; 17: 187-205.
8. Kasper S, Olié JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. Eur Psychiatry. 2002; 3: 331-340.
9. Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. CNS Drugs. 2008; 22: 15-26.
10. Kisa C, Bulbul DO, Aydemir C, Goka E. Is it possible to be dependent to Tianeptine, an antidepresant? A case report. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31: 776-778.
11. Kole MH, Swan L, Fuchs E. The antidepressant tianeptine persistently modulates glutamate receptor currents of the hippocampal CA3 commissural associational synapse in chronically stressed rats. Eur J Neurosci. 2002; 16: 807-816.
12. Lamouchi T, Grira M, Benslamia L, Harzallah MS, Benammou S. Extrapyramidal syndrome worsened by tianeptine. Therapie. 2004; 59: 481-482.
13. Leterme L, Singlan YS, Auclair V, Le Boisselier R, Frimas V. Misuse of tianeptine: five cases of abuse. Ann Med Interne 2003; 154: 58-63.
14. Magariños AM, Deslandes A, McEwen BS. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. Eur J Pharmacol. 1999; 371: 113-122.
15. Novotny V, Faltus F. Tianeptine and fluoxetine in major depression: a 6-week randomised double-blind study. Hum Psychopharmacol. 2002; 17: 299-303.
16. Puig S, Rivot JP, Besson JM. Effects of tianeptine on 5-hydroxyindoles and on the morphine-induced increase in 5-HT metabolism at the medullary dorsal horn level as measured by in vivo voltammetry in freely moving rats. Brain Res. 1993; 600: 219-224.
17. Reagan LP, Hendry RM, Reznikov LR, Piroli GG, Wood GE, McEwen BS et al., Tianeptine increases brain-derived neuro-

trophic factor expression in the rat amygdala. Eur J Pharmacol. 2007; 565: 68-75.
18. Rouby F, Pradel V, Frauger E, Pauly V, Natali F, Reggio P et al., Assessment of abuse of tianeptine from a reimbursement database using 'doctor-shopping' as an indicator. Fundam Clin Pharmacol. 2012; 26: 286-294.
19. Saatçioğlu O, Erim R, Cakmak D. A case of tianeptine abuse. Turk Psikiyatri Derg. 2006; 17: 72-75.
20. Sacchetti G, Bonini I, Weaterloos GC, Samanin R. Tianeptine raises dopamine and blocks stress-induced noradrenaline release in the rat frontal cortex. Eur J Pharmacol 1993; 236: 171-175.
21. Stahl SM. Podstawy psychofarmakologii. Tom 3. Via Medica; Gdańsk 2010
22. Svenningsson P, Bateup H, Qi H, Takamiya K, Huganir RL, Spedding M et al., Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. Eur J Neurosci. 2007; 26: 3509-3517.
23. Tobe EH, Rybakowski JK. Possible usefulness of tianeptine in treatment-resistant depression. Int J Psychiatry Clin Pract. 2013; 17: 313-316.
24. Twardowska K, Rybakowski J. Oś limbiczno-podwzgórzowo-przysadkowo-nadnerczowa w depresji. Psychiatr Pol. 1996; 30: 741-755.
25. Vadachkoria D, Gabunia L, Gambashidze K, Pkhaladze N, Kuridze N. Addictive potential of Tianeptine - the threatening reality. Georgian Med News. 2009; 174: 92-94.
26. Vandel P, Regina W, Bonin B, Sechter D, Bizouard P. Abuse of tianeptine. A case report]. Encephale. 1999; 25: 672-673.
27. Vaugeois JM, Corera AT, Deslandes A, Costentin J. Although chemically related to amineptine, the antidepressant tianeptine is not a dopamine uptake inhibitor. Pharmacol Biochem Behav. 1999; 63: 285-290.
28. Vuković O, Marić NP, Britvić D, Cvetić T, Damjanović A, Prostran M et al., Efficacy, tolerability and safety of tianeptine in special populations of depressive patients. Psychiatr Danub.

Correspondence address:
Ewa Dopierała
Klinika Psychiatrii Dorosłych
ul. Szpitalna 27/33, 60-572 Poznań
phone: +48 661433899
e-mail: dopierala.ewa@gmail.com